Metabolic syndrome risk factor associations with clinical, functional and cognitive outcomes during the first year of treatment in schizophrenia spectrum disorders

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DECLARATION

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This dissertation includes four original papers published in peer reviewed journals or books, and zero unpublished publications. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and for each of the cases where this is not the case a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

Date: December 2020

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SUMMARY

Treatment-emergent metabolic syndrome is an established risk factor for cardiovascular disease known to be associated with cognitive impairment, poor functioning and decreased quality of life in schizophrenia spectrum disorders. However, weight gain and increased lipids have also been correlated with clinical improvement in chronic schizophrenia patients.

While most studies investigating the relationships between body mass and treatment outcome were conducted in patients treated with clozapine and olanzapine, it remains unclear to what extent the role of weight gain as a predictor of favourable clinical outcomes extends to include illness-specific symptom domains in first-episode patients treated with other antipsychotics with a lower obesogenic potential. The effects of other clinical (e.g. sex, substance use, baseline body mass) and treatment-related (e.g. antipsychotic dose, medication adherence) confounders on the above relationships is also unclear. In response to these knowledge gaps, the overarching aim of our doctoral studies was to explore the temporal evolution of metabolic syndrome risk factors and their effects on clinical outcome over 12 months of treatment in first-episode schizophrenia spectrum disorder patients.

We found that an increase in body mass correlates with global psychopathology improvement as well as the disorganized symptoms domain of schizophrenia in first-episode patients (n=106) over 12 months of treatment, independent of the degree of antipsychotic exposure (sub-study I). The association between weight gain and clinical improvement extended to include better overall end-point cognition after 12 months of treatment in our first-episode patient cohort (n=72) (sub-study II). A differential effect for lower baseline body mass index as a predictor of end-point working memory performance was evident in substance users (unfavourable) compared to their non-using counterparts (favourable).

The adverse role of low body mass index as an unfavourable prognostic marker was further substantiated by its associations with an earlier age of psychosis onset and more severe negative symptoms in first-episode patients (n=69) (sub-study III). The inclusion of a diffusion tensor imaging component to our research also revealed a similar differential association of body mass index with fronto-limbic white matter fractional anisotropy (FA) in first-episode patients (low body mass index, low FA) versus healthy controls (high body mass index, low FA) adjusting for age and sex (sub-study III). Extension of our structural neuroimaging research to include brain structures involved in the physiological, hedonic and cognitive control as part of a "core eating network" further identified smaller anterior hippocampal volumes as a sex-specific predictor of weight gain in first-episode patients (n=90) (sub-study IV).

Our research supports the role of weight gain as a predictor of favourable clinical outcomes in first-episode schizophrenia patients for whom treatment adherence is assured. In contrast, low body mass and by extension failure to gain weight could represent an unfavourable prognostic marker in first-episode patients, particularly those who use substance users. Future studies would do well to combine clinical, biological and neuroimaging data in order to characterize intrinsic metabolic profiles in relation to long-term treatment outcomes in first-episode schizophrenia.

OPSOMMING

Metaboliese sindroom sekondêr to behandeling is ’n belangrike risikofaktor vir kardiovaskulêre siekte wat verbind word met kognitiewe aantasting, swak funksionering en ’n afname in lewensgehalte by skisofrenie spektrum steurings. ’n Toename in gewig en lipiede is egter ook al verbind met kliniese verbetering in pasiënte met chroniese skisofrenie.

Terwyl meeste studies wat die verhouding tussen liggaamsmassa en uitkoms ondersoek gedoen is met pasiënte wat met klosapien en olansapien behandel is, is dit onduidelik tot watter mate die rol van gewigstoename as ’n voorspeller van gunstige kliniese uitkomste verder strek om siekte-spesifieke simptoomdomeine in te sluit in eerste-episode pasiënte wat met ander antipsigotiese middels met ’n laer obesogeniese potensiaal behandel word. Die uitwerking van ander kliniese (bv. geslag, middelgebruik, basislyn liggaamsmassa) en behandelings-verwante (bv. die dosis van antipsigotiese middels, hoe getrou medikasie gebruik word) faktore op bogenoemde verband is ook onduidelik. In reaksie op hierdie leemtes in kennis was die oorkoepelende doel van die doktorale studie om die temporele ontwikkeling van risikofaktore vir metaboliese sindroom te ondersoek asook die uitwerking daarvan op kliniese uitkoms oor 12 maande van behandeling in pasiënte met ’n eerste-episode van skisofrenie spektrum steurnisse.

Ons het gevind dat ’n toename in liggaamsmassa verband hou met algemene psigopatologiese verbetering sowel as die gedisorganiseerde simptoomdomein van skisofrenie in eerste-episode pasiënte (n=106) oor 12 maande van behandeling, onafhanklik van die graad van antipsigotiese blootstelling (substudie I). Die verband tussen gewigstoename en kliniese verbetering het ook beter algemene eindpunt kognisie na 12 maande van behandeling in ons groep eerste-episode pasiënte ingesluit (n=72) (substudie II). Daar was ook ‘n differensiële effek vir laer basislyn liggaamsmassaindeks as ’n voorspeller van eindpunt-werkgeheue prestasie in middelgebruikers (ongunstig) in vergelyking met nie-gebruikers (gunstig).

Die nadelige rol van lae liggaamsmassaindeks as ’n ongunstige prognostiese merker was ook gestaaf deur die verbintenis daarvan met ’n vroeër ouderdom waarop psigose begin het en ernstiger negatiewe simptome in eerste-episode pasiënte (n=69) (substudie III). Die insluiting van ’n diffusie tensor beelding komponent by ons navorsing het ook ’n soortgelyke onderskeidende verbintenis onthul tussen liggaamsmassaindeks en fraksionele anisotropie (FA) van frontaal-limbiese witstof in eerste-episode pasiënte (lae liggaamsmassaindeks, lae FA) teenoor gesonde kontroles (hoë liggaamsmassaindeks, lae FA) met aanpassings vir ouderdom en geslag (substudie III). ’n Uitbreiding van ons navorsing oor strukturele neurobeelding om breinstrukture in te sluit wat betrokke is by fisiologiese, hedoniese en kognitiewe beheer as deel van ’n “kern-eetnetwerk” het kleiner volumes van die anterior hippokampus verder geïndentifiseer as ’n geslag-spesifieke voorspeller van gewigs toename in eerste-episode pasiënte (n=90) (substudie IV).

Ons navorsing ondersteun die rol van gewigstoename as ’n voorspeller van gunstige kliniese uitkomstes in pasiënte met ’n eerste episode van skisofrenie wie se getroue volging van behandeling verseker word. In teenstelling hiermee kan ’n laer liggaamsmassa en by uitbreiding die versuim om gewig aan te sit ’n ongunstige prognose merker wees in eerste-episode pasiënte, veral in die wat middels gebruik. Dit sal goed wees as toekomstige studies kliniese, biologiese en neurobeeldings data kan kombineer met die oogmerk om intrinsieke metaboliese profiele te identifiseer met betrekking tot langtermyn uitkoms in eerste-episode skisofrenie.

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CHAPTER ONE

INTRODUCTION

1.1. BACKGROUND

This chapter provides a contextualized overview of the research topic for doctoral studies described in this dissertation, focusing on the associations between weight gain and treatment outcome in first-episode schizophrenia spectrum disorders. The problem statement and study rationale are then described, followed by a formulation of the research aim, corresponding study objectives, and relevant hypotheses. The structure of the dissertation is also outlined, followed by a description of the research contributions of the doctoral candidate.

1.1. Weight Gain in First-Episode Schizophrenia

Individuals living with schizophrenia are at an elevated risk for early demise, translating into an approximately 10-25 year lower life expectancy (Saha et al., 2007; Laursen et al., 2012). There are multiple reasons for the increased mortality gap evident between schizophrenia patients and the general population, including accidental causes such as suicide, as well as a higher prevalence of substance abuse (Laursen et al., 2012). In particular, comorbid illnesses such as cardiovascular disease are recognized as a major cause of premature death in schizophrenia spectrum disorders (Hennekens et al., 2005; Saha et al., 2007).

In this context, the metabolic syndrome and its constituent components are well-known risk factors for ischemic heart disease and adverse cardiac events both in schizophrenia patients and non-affected individuals (Hennekens et al., 2005). In addition to genetics, lifestyle and dietary factors, antipsychotic use has emerged as a notable cause of treatment-emergent metabolic syndrome in schizophrenia spectrum disorders (Riordan et al., 2011; Mitchell et al., 2013). There is marked variation in the metabolic side-effect profiles of different antipsychotics (de Hert et al., 2012; Pillinger et al., 2020). The second-generation drugs clozapine and olanzapine are particularly well known for their high propensity to induce weight gain and associated metabolic changes (de Hert et al., 2012; Mitchell et al., 2013). However, most antipsychotics used to treat schizophrenia are now known to cause weight

gain if treatment exposure is sufficient (de Hert et al., 2012; Bak et al., 2014). Indeed, other medications such as zipradisone, despite an apparent favourable effect on lipid profiles, have been linked to the development of non-alcoholic fatty liver disease as the hepatic expression of the metabolic syndrome (Morlan-Coarasa et al., 2016).

In first-episode schizophrenia patients, initial short-term exposure to treatment confers significant risk for weight gain (Mitchell et al., 2013). In many cases, weight gain is expected to be early and pronounced, developing as soon as two weeks after the initiation of antipsychotic treatment (Chadda et al., 2013), and most commonly being clinically apparent within the first six months of therapy (Attux et al., 2007). Further metabolic deterioration is often rapid, particularly if compounded by co-treatment with mood stabilizers or antidepressants (Bioque et al., 2018). Initial short-term studies reported that weight gain in first-episode cases levels off or stops within the first to second year of treatment (Umbricht et al., 1994; Allison et al., 2009). While long-term outcome data remains scarce, there is also evidence to suggest that weight gain continues for years or even decades after the initiation of treatment (Strassnig et al., 2017). The risk for other metabolic complications such as Insulin Resistance (IR) and type II Diabetes Mellitus (DM II) increases significantly with ongoing antipsychotic use (Jeong et al., 2018) and is primarily elevated over the long-term, chronic course of treatment (Pillinger et al., 2017).

The development of weight gain and associated metabolic syndrome changes over the course of antipsychotic treatment is therefore a common occurrence in first-episode schizophrenia spectrum disorders. However, certain metabolic syndrome abnormalities are already present in treatment-naive patients (Freyberg et al., 2017). Indeed, several cross-sectional studies have reported a higher prevalence of metabolic syndrome as composite entity in first-episode patients versus controls (Darcin et al., 2015; Fawzy et al., 2015). However, this finding has not been replicated in all studies to date (Chiliza et al., 2015a; Rawat et al., 2018). Nevertheless, a majority of schizophrenia patients (~60%) will present with at least one feature of the metabolic syndrome at baseline (Verma et al., 2009; Bioque

et al., 2018) even if full diagnostic criteria are not met. In particular, systematic reviews and meta-analyses support the existence of increased waist circumference, impaired glucose tolerance and lipid abnormalities consistent with the metabolic syndrome in first-episode patients with minimal prior treatment exposure (Petrikis et al., 2015; Misiaket al., 2017; Pillinger et al., 2017; Petruzzelli et al., 2018). Metabolic syndrome abnormalities have also been described in first-degree relatives of patients with schizophrenia (Darcin et al., 2015; Jensen et al., 2017; Choiunard et al., 2018) as well as individuals at clinical high-risk for developing a first-episode of psychosis (Cordes et al., 2017).

From converging lines of evidence, studies to date could support the notion that certain metabolic syndrome features known to arise secondary to pharmacotherapy in schizophrenia patients, are already present in first-episode, treatment-naive cases. In this context, certain metabolic syndrome features present in treatment-naive patients might be considered as intrinsic to the illness itself (Freyberg et al., 2017).

1.2. Body Mass and Treatment Outcome in First-Episode Schizophrenia

Treatment-emergent metabolic syndrome is thus recognized as an important contributor to excess mortality risk in schizophrenia (Hennekens et al., 2005; Saha et al., 2007). This motivates the need to predict both clinical outcome and side-effect burden in affected patients (Riordan et al., 2011). Indeed, failure to detect and manage metabolic syndrome risk factors early on could increase the chance for poor long-term outcomes as the illness progresses (Vancampfort et al., 2015). On the one hand, risk for the development of metabolic syndrome is increased in chronic compared to first-episode schizophrenia patients (Vamcampfort et al., 2013). On the other, first-episode patients are also at substantial risk for weight gain, despite showing an overall favourable response to treatment (Karson et al., 2016). It is therefore important for clinicians to balance clinical efficacy with the mitigation of treatment-emergent side-effects including metabolic syndrome changes irrespective of the stage of illness (Lappin et al., 2018).

Cardiovascular risk monitoring is thus often incorporated as a component of patient care in an attempt to mitigate or prevent treatment-emergent metabolic syndrome changes (Phutane et al., 2011). International guidelines are also now in place to support the more widespread adoption of screening and monitoring programs for cardio-metabolic risk factors, which remain both under-diagnosed and undertreated in chronic schizophrenia (Ventriglio et al., 2015; Lappin et al., 2018). Emphasis is often placed on extensive metabolic risk screening and monitoring following initial exposure to treatment, viewed as a "critical period for prevention" of cardiovascular disease (Phutane et al., 2011). In an attempt to guide clinicians, much research has been conducted in an attempt to identify, characterize and validate accurate, appropriate and cost-effective predictors of treatment outcome in schizophrenia (Carbon and Correll 2014; Santesteban-Echarri et al., 2017). Interestingly, since antipsychotics with a high potential to induce weight gain are often those with superior clinical efficacy in resistant cases of schizophrenia (Leucht et al., 2013), socio-demographic and clinical predictors of clinical response often overlap with those for metabolic side-effects (Pillinger et al., 2020). However, very little is known about the role of anthropometric, metabolic, biological and blood-based biomarkers in the prediction of clinical outcome in first-episode schizophrenia (Fond et al., 2015; Mondelli et al., 2015).

Nevertheless, there is evidence to suggest that antipsychotic-induced metabolic syndrome changes including weight gain influence the clinical response to treatment both in first-episode (Nettis et al., 2019) and chronic schizophrenia (Godin et al., 2018). In a similar fashion, increased body mass has been correlated with disease chronicity, rapid cycling, a longer duration of illness, treatment non-response, and poorer functional outcomes in bipolar disorder (Fagiolini et al., 2003; Calkin et al., 2009, 2015). In addition, some (Green et al., 2017) but not all (Angstman et al., 2013; Mansoor et al., 2013; Sahle et al., 2019) studies have identified weight gain as a predictor of treatment outcome in patients with major depressive disorder. The purported unfavourable association of metabolic syndrome changes with adverse clinical outcomes in schizophrenia spectrum disorders appears

intuitive. After all, studies have often linked metabolic syndrome risk factors with more severe prodromal symptoms in those at-risk for schizophrenia (Cadenhead et al., 2019), earlier age of onset in newly diagnosed patients (Nadalin et al., 2018), as well as more severe negative psychopathology, and deficit-type symptoms in chronic schizophrenia (Arango et al., 2008, 2011; Sicras-Mainar et al., 2014). In a similar fashion, antipsychotic-induced metabolic changes including weight gain have been shown to negatively affect physical health, cognitive outcomes, level of functioning and quality of life in chronic patients (Agid et al., 2013; Kritharides et al., 2017).

However, there is an opposing body of evidence which rather positions increased body mass as a favourable prognostic marker in the management of schizophrenia. This notion, while apparently counterintuitive, is not without merit. Indeed, Bleuler was among the first to describe abnormalities of appetite and eating behaviours in schizophrenia back in the 19th century (Hoff, 2012). In the early 20th century, reports of an association between spontaneous recovery and weight gain started to emerge (Kalinowsky, 1948). It was during the era of first-generation antipsychotics that the potential role of weight gain as a favourable predictor of treatment response fully started to emerge (Planansky, 1958). In more recent decades, further evidence has emerged to suggest that weight gain related to antipsychotic use is associated with general clinical improvement and overall therapeutic benefit (Sharma et al., 2014).

In a systematic review of 31 independent research studies conducted by Raben and colleagues (2017), the authors demonstrated a favourable association between weight gain and clinical outcome, which was largely independent of age, sex, level of compliance, and prior exposure to treatment, i.e. also being present in first-episode patients. In comparison, both the use of second-generation antipsychotics with a high obesogenic potential (i.e. clozapine, olanzapine) and the duration of current treatment moderated the relationship between weight gain and clinical improvement (Raben et al., 2017). In a more recent systematic review and meta-analysis of 100 randomized controlled trials conducted by

Pillinger et al., (2020), the authors also demonstrated that an increase in body mass index correlated with an incremental reduction in global psychopathology. In summary, metabolic assessment may have important implications for the management of schizophrenia beyond its more established role in cardiovascular risk management. In particular, cardio-metabolic risk assessment could help guide and optimize patient care by facilitating the identification of important prognostic subtypes (Freyberg et al., 2017).

1.3. **Problem Statement and Study Rationale**

Several important challenges remain in establishing the prognostic relevance of metabolic syndrome and its constituent components as markers of treatment outcome in schizophrenia spectrum disorders.

First, most studies reporting an association between weight gain and clinical improvement have focused on global measures of illness severity in chronic patients treated with the second-generation antipsychotics clozapine and olanzapine (Sharma et al., 2014; Raben et al., 2017). It is therefore unclear whether the purported favourable effects of weight gain on clinical outcome are illness-specific, and extend to include first-episode patients treated with other antipsychotics.

Second, the majority of prior outcome studies have not comprehensively accounted or controlled for either the degree of treatment exposure, or adherence to medication. This is important, since weight gain may be a risk factor for treatment non-adherence. On the other hand, higher rates of adherence may be related to the clinical efficacy of treatment, but also a greater likelihood of metabolic side-effects including weight gain, which in turn again poses risk for non-compliance (Higashi et al., 2013). Despite differences in metabolic risk profile across antipsychotics of different classes, the formulation of a specific medication (oral vs. long-acting injectable antipsychotic) does not appear to constitute a major individual differentiating factor in the prediction of risk for metabolic syndrome (Ventriglio et al., 2018).

Third, it remains unclear to what extent researchers should consider the manner in which baseline metabolic status could influence the inter-play between treatment-emergent metabolic syndrome changes, symptom trajectories and attainment of meaningful clinical outcomes (Raben et al., 2017). This topic warrants attention, since metabolic syndrome risk factors are not only common in schizophrenia patients, but appear to cluster based on specific clinical traits (Arango et al., 2008, 2011; Nadalin et al., 2018; Cadenhead et al., 2019). In particular, the apparent overlap between increased body mass and negative symptoms irrespective of disease stage could have important implications for treatment (Sicras-Mainar et al., 2014; Mezquida et al., 2018).

Lastly, the different factors underscoring the purported relationships between weight gain and different clinical, cognitive as well as functional aspects of outcome remain incompletely described. There is particular interest in biological and molecular mechanisms such as oxidative stress, chronic, low-grade inflammation (Mondelli and Howes 2014; Haring et al., 2015), hypothalamic-pituitary-adrenal axis dysregulation (Mondelli and Pariante 2008) and abnormal regulation of hormones and adipokines involved in the regulation of appetite and satiety (Basoglu et al., 2010). In particular, little is known about the role of brain structure and white matter connectivity in relation to pre-treatment body mass, weight gain and clinical outcome in schizophrenia patients. This is important, since earlier studies have reported an association between metabolic syndrome risk factors and brain volumetric changes in first-episode schizophrenia spectrum disorders over initial exposure to treatment (Emsley et al., 2015).

1.4. Aims and Objectives

In response to these research challenges, the overarching aim of the doctoral studies described in this dissertation was to **explore the temporal evolution of metabolic syndrome risk factors and their effects on clinical outcome over the first year of treatment** in schizophrenia spectrum disorders in relation to their brain structural and white matter concomitants.

The specific research objectives were as follows:

- To examine the associations between treatment-emergent metabolic syndrome changes and psychopathology improvement over 12 months of treatment in first-episode schizophrenia spectrum disorder patients in relation to age, sex, ethnicity, substance use, baseline metabolic status, and the degree of antipsychotic exposure (sub-study I)
- To examine the associations between change in body mass over 12 months and end-point cognitive performance in first-episode schizophrenia spectrum disorder patients in relation to age, sex, substance use, baseline metabolic status, and the degree of antipsychotic exposure (sub-study II)
- To examine the associations of body mass with brain structure and connectivity in first-episode schizophrenia spectrum disorder patients compared to otherwise healthy matched controls. In particular, we focused on fronto-limbic white matter tracts known to connect brain regions involved in the regulation of metabolism, appetite, satiety and reward as part of a “core eating network” (sub-study III)
- To examine the associations of brain volumes for sub-cortical regions (including the thalamus, pallidum, putamen, caudate, ventral diencephalon, brainstem, amygdala, hippocampus, and nucleus accumbens) involvement in the cognitive, hedonic, emotional and physiological control of feeding behaviours in humans with weight gain trajectories over the first 12 months of treatment (sub-study IV)

1.5. Study Hypotheses

1. Weight gain over the first 12 months of treatment in first-episode schizophrenia spectrum disorder patients will be associated with psychopathology improvement, largely independent of the degree of antipsychotic exposure (sub-study I)
2. The association of weight gain with clinical improvement over the first 12 months of treatment in first-episode schizophrenia spectrum disorder patients will extend to include better end-point cognition (sub-study II)
3. Lower baseline body mass will be differentially associated with fronto-limbic white matter fractional anisotropy (FA) in first-episode schizophrenia spectrum disorder patients (decreased body mass, decreased FA) versus healthy controls (increased body mass, decreased FA) for tracts which connect brain regions known to form part of a “core eating network” in humans (sub-study III)
4. Impairment in brain structure and integrity at baseline will predict greater weight gain over the first 12 months of treatment in first-episode schizophrenia spectrum disorder patients, particularly for sub-cortical regions involved in the control of appetite, satiety, and reward (sub-study IV)

1.6. Outline and Structure of Dissertation

The doctoral research described here was conducted as part of a larger single-site cohort study developed in order to explore the clinical, biological and functional aspects of treatment outcome in first-episode schizophrenia spectrum disorder patients. This parent project (EONCKS), first conceived and initiated in 2007, was named after the principal investigators of the study, viz. Professors Robin Emsley, Piet Oosthuizen, Dana Niehaus, Liezl Koen, Bonginkosi Chiliza, and Renata Schoeman. The first round of data collection was completed in 2011, which included comprehensive patient evaluation and follow-up over regular visits.

In the this dissertation, research conducted over the course of my doctoral studies has been integrated and presented in the form of journal articles, all of which have been published in high-impact international journals (Table 1). In brief, the research described here is based around the temporal evolution of metabolic syndrome risk factors and their associations with clinical outcome over the first 12 months of treatment in schizophrenia spectrum disorder patients in relation to relevant brain structural concomitants. This research focus was motivated by the observation that initial exposure to treatment with flupenthixol decanoate in an overlapping first-episode patient cohort (n=107) resulted in significant weight gain, as well as elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol levels (Chiliza et al., 2015a). In addition, our focus on the effects of metabolic syndrome risk factors on clinical outcome was substantiated by the association evident between low body mass index and treatment non-response in first-episode schizophrenia spectrum disorders (n=126) (Chiliza et al., 2015b). Lastly, the decision to incorporate a neuroimaging component as part of the present research project was motivated by evidence from an initial pilot project, in which first-episode patients (n=22) exposed to three months of treatment with flupenthixol decanoate demonstrated an increase in body mass index, which in turn correlated with bilateral volume reductions in the ventral diencephalon (Emsley et al., 2015).

For each publication, I led the development of a research question and paper proposal, performed the initial statistical analyses, drafted the first manuscript, as well as edited and finalized the article for submission following co-author input. In addition, I assisted with pre- and post-processing of structural imaging data for the relevant studies of interest. In each sub-study, I was further presented with individual opportunities for research capacity and skills development. In particular, I focused on training in statistical analysis and interpretation, including linear regressions (Chapters II, III, and V), mixed effects models for continuous repeated measures (Chapter V), and multivariate analyses of covariance (Chapter IV).

Chapter II is a first-author journal article published in the international journal Schizophrenia Research. In this publication, we describe a sub-study (I) in which we explored the associations between pre-treatment as well as treatment-emergent metabolic syndrome changes and psychopathology improvement over 12 months of treatment in first-episode schizophrenia spectrum disorder patients (n=106). To the best of our knowledge, this was the first study to demonstrate that treatment-emergent weight gain is associated with psychopathology improvement in first-episode patients treated with a relatively weight-neutral depot antipsychotic, independent of age, sex, substance use, and the degree of antipsychotic exposure. This study provided the scientific rationale for further exploration of weight gain in relation to treatment outcomes in our patient cohort.

Chapter III is a first-author journal article published in the international journal Metabolic Brain Disease. In this publication, we describe a sub-study (II) in which we sought to extend our initial research focus (Chapter II) to include the associations of body mass and weight gain with cognitive performance in first-episode schizophrenia spectrum disorder patients (n=72). We demonstrated that, in addition to psychopathology improvement, weight gain is associated with better end-point cognitive performance and the working memory domain over 12 months of treatment, independent of age, sex, and the degree of antipsychotic exposure. Importantly, low baseline body mass index was associated with better end-point

working memory performance in substance non-users, who gained significant body weight over the course of treatment. In contrast, high baseline body mass index appeared to have a protective effect in substance users, who showed prevalent weight loss, and a less pronounced increase in body weight, over the course of treatment.

Chapter IV is a first-author journal article published in the international journal Psychiatry Research: Neuroimaging. In this publication, we describe a sub-study (III) in which we examined the neurobiological and brain white matter structural correlates of body weight in first-episode schizophrenia spectrum disorder patients (n=69) versus healthy controls (n=93). We showed that baseline body mass index is differentially associated with fronto-limbic white matter fractional anisotropy (FA) in the two groups, with particular involvement of the corpus callosum (genu) and tapetum in patients (low body mass index, low FA) versus controls (high body mass index, low FA). In addition, lower body mass index was significantly correlated with an earlier age of onset as well as more severe negative symptoms, which were also inter-related. This study provided important evidence substantiating the involvement of brain structural integrity and connectivity underscoring the relationship between body mass and symptom expression in our first-episode patient sample.

Chapter V is a first-author journal article published in the international journal Psychiatry Research: Neuroimaging. In this publication, we sought to build on our research described above by investigating the associations of body mass and weight gain with brain volumetric measures for sub-cortical regions implicated in the physiological (e.g. hypothalamus), cognitive-emotional (e.g. orbito-frontal and dorso-lateral prefrontal cortex, hippocampus, amygdala) and hedonic (e.g. ventral tegmental area, nucleus accumbens) control of eating (Chen et al., 2016) in first-episode patients (n=90) versus healthy controls (n=92). In this sub-study (IV), we focused on the hippocampus, a key brain region involved in the regulation of most aspects of eating behaviours in humans, and its individual subfields. Importantly, we demonstrated a significant interactive effect between sex and anterior hippocampus size as

predictors of change in body mass over 12 months, adjusting for age, substance use, and treatment duration. In an exploratory post-hoc sub-analysis, partial correlations showed a significant association between weight gain and smaller CA1, CA3 and subiculum volumes in females, but not males, adjusting for age and substance use, with similar trends evident for the CA4 and presubiculum subfields.

Chapter VI presents a narrative synthesis of the most important insights gathered as a result of the doctoral research described in this dissertation. Future avenues for both local and international research are also discussed, and an overall conclusion provided.

Table 1. Outline of sub-studies published as original first-author manuscripts in high-impact international journals. Information on the participants, relevant neuroimaging modality, and research objective guiding the relevant research is also provided.

Manuscript	Publication status	Participants	Neuroimaging modality	Research objective
Chapter II Weight gain and metabolic change as predictors of symptom improvement in first-episode schizophrenia spectrum disorder patients treated over 12 months	Published	106 patients	N/A	1
Chapter III Relationship between changes in metabolic syndrome constituent components over 12 months of treatment and cognitive performance in first-episode schizophrenia	Published	72 patients	N/A	2
Chapter IV Fronto-limbic white matter fractional anisotropy and body mass index in first-episode schizophrenia spectrum disorder patients compared to healthy controls	Published	69 patients 93 controls	DTI	3
Chapter V Hippocampal subfield volumes and change in body mass index over 12 months of flupenthixol decanoate treatment in first-episode schizophrenia spectrum disorders	Published	90 patients 92 controls	sMRI Brain volume	4

DTI= diffusion tensor imaging; N/A= not applicable; sMRI= structural magnetic resonance imaging

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CHAPTER TWO

Weight gain and metabolic change as predictors of symptom improvement in first-episode schizophrenia spectrum disorder patients treated over 12 months

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Weight gain and metabolic change as predictors of symptom improvement in first-episode schizophrenia spectrum disorder patients treated over 12 months

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ABSTRACT

Background: Treatment-emergent weight gain is associated with antipsychotic efficacy in schizophrenia patients treated with clozapine and olanzapine. However, few studies have investigated this relationship in first-episode patients treated with other antipsychotics, in particular those with a lower obesogenic potential.

Aim

To investigate the relationships between weight gain and associated metabolic changes with psychopathology improvement in relation to age, sex, ethnicity, substance use, treatment duration and antipsychotic dose in first-episode schizophrenia spectrum disorder patients.

Methods: This single site cohort study included 106 minimally treated or antipsychotic-naive patients treated with flupenthixol decanoate over 12 months. Psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) and BMI, fasting blood lipids and glucose were assessed at regular intervals. Linear regression models were constructed to determine the effects of socio-demographic, clinical and metabolic factors as predictors of change in total PANSS score and factor-derived domains.

Results: BMI change scores were inversely correlated with change in PANSS total ($R = -0.25$; $p = 0.011$), positive ($R = -0.23$; $p = 0.019$), depressive anxiety ($R = -0.21$; $p = 0.031$) and disorganized symptoms ($R = -0.32$; $p < 0.001$). Linear regression analysis showed that increased BMI and treatment duration both predicted improvement in global psychopathology and disorganized symptoms independent of age, sex, ethnicity, substance use, co-medication with antidepressants and/or anticholinergics, as well as the dose and duration of antipsychotic exposure.

Conclusions: Our findings suggest that the relationship between treatment-emergent weight gain and psychopathology improvement is not limited to patients treated with antipsychotics most associated with weight gain, and is not confounded by treatment duration and dose.

1. Introduction

An increased prevalence of weight gain and metabolic syndrome in schizophrenia spectrum disorders contributes to elevated risk for cardiovascular disease (CVD) which is associated with excess morbidity and mortality (Riordan et al., 2011). In addition to diet, lifestyle and genetic factors, antipsychotic use has emerged as a major contributor to the higher risk for treatment-emergent metabolic syndrome evident for schizophrenia (Saha et al., 2007; Emul and Kalelioglu, 2015) even in first-episode cases (Tek et al., 2016). The high obesogenic potential of several second-generation antipsychotics is well known, with these drugs also posing an independent risk for metabolic changes associated with obesity (Falissard et al., 2011; Leucht et al., 2013). A recent meta-analysis (Bak et al., 2014) confirms that these changes are not limited to the second-generation antipsychotics and that almost all antipsychotics are associated with weight gain given sufficient treatment exposure. Indeed, certain metabolic abnormalities including hypertension may be more pronounced in patients treated with first-generation antipsychotics (Falissard et al., 2011), underscoring the need for early assessment and monitoring of cardio-metabolic risk in first-episode schizophrenia irrespective of antipsychotic type.

Several early studies dated prior to the introduction of second-generation antipsychotics (Planansky, 1958; Klett and Caffey Jr, 1960) suggested the prognostic importance of weight gain as a marker of favourable treatment outcome. Multiple subsequent studies have also reported that weight gain is associated with decreased global and

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general psychopathology in adult schizophrenia spectrum disorder patients, particularly those treated with clozapine and olanzapine (Sharma et al., 2014). Elevated serum lipids associated with antipsychotic use may also predict psychopathology improvement in acute and long-term settings (Lally et al., 2013; Solberg et al., 2015, 2016). Finally, greater reduction in global psychopathology has been correlated with weight gain (Kemp et al., 2013) and metabolic syndrome (Grover et al., 2016) in adolescent schizophrenia patients. A recent systematic review reported a link between antipsychotic-induced weight gain and therapeutic benefit in 22 (71%) of the 31 independent studies investigated, which collectively included 6063 patients with schizophrenia and related severe mental illnesses (Raben et al., 2018). These findings are in accordance with those reported in a previous review by Sharma et al. (2014) which reported an association between treatment-emergent metabolic changes and antipsychotic efficacy in 14 of the 15 studies evaluated. These systematic review findings support a relationship between weight gain and psychopathology improvement in schizophrenia patients independent of age, sex, ethnicity and prior antipsychotic use. The findings also raise the possibility of a potential shared mechanistic pathway between metabolic changes induced by weight gain and antipsychotic efficacy (Venkatasubramanian et al., 2013).

However, the relationship of metabolic syndrome to disease severity and clinical outcome remains incompletely described (Blin and Micallef, 2001). Several studies have failed to replicate a correlation between antipsychotic-induced weight gain and psychopathology improvement (Umbricht et al., 1994; Hummer et al., 1995). Further, the majority of reported associations of weight gain to date have been with global and general psychopathology, while mixed results were reported for positive and negative symptoms (Czobor et al., 2002; Procyshyn et al., 2007), and the illness-specificity of these findings has been questioned. In addition, the causal basis for such a relationship remains unclear, as reports of an association between weight loss and exacerbation of psychosis are conflicting (Chen et al., 2014; Chukhin et al., 2016). In addition, it remains unclear whether switching to antipsychotics with a lower obesogenic potential influences the effect of weight gain on treatment outcomes. Outcome studies to date are further limited by important confounders including variable treatment end-points and inconsistent approaches to dealing with dropouts, non-standardised antipsychotic treatment of patients, not assessing the role of adherence, and including chronic schizophrenia samples where previous medication and illness chronicity may affect outcome (Raben et al., 2018). Lastly, the potential modulating effects of add-on treatment such as antidepressants (Terevnikov et al., 2013; Lu et al., 2017) have not been extensively considered.

There is a critical lack of evidence from prospective longitudinal studies assessing the relationships between treatment-emergent weight gain/metabolic changes and treatment response in patients treated with antipsychotics other than the more commonly studied second generation drugs clozapine and olanzapine represented in most investigations to date. Importantly, most studies to date have also failed to control for adherence and compliance in a systematic fashion, in addition to limiting investigation to the acute stage of treatment, typically less than six months duration (Raben et al., 2018). It is also not always clear whether duration of treatment exposure has been considered. However, it stands to reason that patients with greater antipsychotic exposure are likely to gain more weight, and at the same time show greater reduction of symptoms. In addition, with the exception of limited early studies of schizophrenia patients treated with haloperidol (Bustillo et al., 1996), no studies have explored the link between weight gain and psychopathology improvement in first-episode patients treated with relatively "weight-neutral" (e.g. aripiprazole, ziprasidone) or depot (e.g. flupenthixol decanoate) antipsychotics. To the best of our knowledge, no outcome studies have further sought to evaluate the relationships with particular symptom domains consistently identified using factor analyses (Emsley et al., 2003; Jerrell and Hrisko, 2013).

In a previous study (Chiliza et al., 2015), we used linear mixed effects for continuous repeated measures (MMRM) to demonstrate a significant visit-wise increase in body mass index (BMI) in antipsychotic-naïve or minimally treated first-episode schizophrenia patients (n = 107) over 12 months of standardised treatment with flupenthixol decanoate, independent of age, sex, and end-point antipsychotic dose. In the present study, we sought to build on these existing findings by evaluating the relationships between treatment-emergent weight gain, metabolic changes and psychopathology improvement, drawing from the abovementioned patient cohort. In this context, we focused on linear regression analysis selected as the most appropriate statistical approach to establishing the effects of metabolic change scores as predictors of change in psychopathology over the course of antipsychotic treatment in relation to socio-demographic, clinical and treatment-related covariates.

2. Materials and methods

2.1. Study design and ethics approval

This was a single-site longitudinal study which recruited antipsychotic-naïve or minimally treated patients with first-episode schizophrenia spectrum disorders (schizophrenia, schizophreniform or schizoaffective disorder). Ethical approval was obtained from the Health and Research Ethics Committee (HREC) at Stellenbosch University (SU) (N06/08/148). Written, informed consent was obtained from participants and where appropriate, from a legal guardian. Our study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines (International Conference on Harmonization, 1996).

2.2. Selection of study participants

Study participants were selected, as part of an ongoing study, from first admissions to hospitals and community clinics in the metro and rural areas of North Eastern Cape Town, the Winelands and the West Coast over a four year period (2007–2011). Inclusion criteria were men and women, in- or out- patients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria were: lifetime exposure to >4 weeks of antipsychotic medication, serious or unstable medical condition, psychosis arising from acute substance intoxication, and intellectual disability.

2.3. Antipsychotic treatment

Patients were treated according to a fixed protocol with flupenthixol decanoate. First-choice treatment with a depot antipsychotic was based on evidence that their greatest benefits may be observed early in the illness by improving adherence and preventing accruing morbidity, as well as their demonstrated efficacy and tolerability in this population (Chue and Emsley, 2007). We chose flupenthixol decanoate as the best-tolerated depot that was available in the public sector in South Africa. There was a seven-day lead-in with oral flupenthixol 1–3 mg/day followed by flexible doses of flupenthixol decanoate. The starting dose was 10 mg IM 2-weekly. The lowest possible dose was maintained, and only increased when an insufficient response persisted. Additional oral flupenthixol was permitted, but seldom prescribed. Permitted concomitant medications included lorazepam, biperidin, orphenadrine, propranolol and antidepressants. In order to minimize the potential effects of additional treatment on metabolic status, benzodiazepines, anticholinergics and propranolol were not allowed within 12 h of the time of assessment. Prohibited medications included other antipsychotics, mood stabilizers and psychostimulants.

2.3.1. Clinical assessments

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994) and psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Evaluation of psychopathology symptom categories was performed by calculating PANSS factor analysis-derived domains (i.e. positive, negative, depressive-anxiety, disorganized and exhibition-hostility symptoms) (Emsley et al., 2003). Remission status was also assessed using the Remission in Schizophrenia Working Group (RSWG) consensus criteria proposed by Andreasen et al. (2005).

2.3.2. Metabolic assessments

A physical examination was performed at baseline and study completion. Body weight was measured at baseline, week 6, and months 3, 6, 9 and 12. Patients removed all surplus clothing including their socks and shoes and were weighed on an electronic scale that was regularly calibrated throughout the study. Height was measured with a pre-fixed wall-mounted measuring tape. Body mass index (BMI) was also calculated as the patient's body weight in kilograms (kg) divided by their height in meters squared (m^2). While we also measured waist circumference, we did not use this in the analyses, due to a large number of missing values (n = 26, 25%). Systolic (SBP) and diastolic (DBP) blood pressures were assessed at baseline and at months 3, 6 and 12. A peripheral venous blood sample was collected from participants following an eight hour fasting period and ten minute rest prior to venepuncture. Biochemical testing was performed at baseline and again at months 3, 6, 9 and 12, and included assessment of the fasting lipid profile (triglycerides, total, LDL and HDL cholesterol) and glucose levels.

2.3.3. Urine toxicology

Urine toxicology was performed at baseline and again at months 3, 6 and 12 to assess use of cannabis, methaqualone and methamphetamine over the course of the study. Patients who tested positive on any occasion were classified as substance use positive.

2.4. Statistical analysis

Statistical analyses were performed using the R Studio software package. All participants with at least one baseline and one follow-up measure were included for analysis. End-point scores were calculated by last observation carried forward. Clinical and metabolic change scores were calculated by subtracting the baseline score from the end-point score. Descriptive statistics and graphical summaries were used to assess whether the key variables meet standard assumptions for the planned analyses and to identify outliers. Non-normal data was log-transformed prior to analysis. Categorical variables were described using cross-tabulation and frequency tables and compared between study groups using the Pearson's Chi-Squared or Fisher's exact tests. Normality of distribution for numerical variables was established using the Shapiro-Wilk test. For normally distributed data, quantitative phenotypes were described as the means along with standard deviation (SD) and compared between study groups using a Student's *t*-test. Linear correlations were described using the Pearson's correlation or Spearman's rank correlation as applicable. Post-hoc Bonferroni corrections were performed where applicable to correct for multiple comparisons across the six psychopathology domains of interest (i.e. PANSS total score as well as positive, negative, disorganized, depressive-anxiety and excitement-hostility domains). Linear regression models were constructed to evaluate the role of metabolic change scores as predictors of psychopathology improvement in relation to socio-demographic (age, sex, ethnicity), clinical (substance use) and treatment-related (antipsychotic dose, treatment duration, antidepressant and/or anticholinergic co-medication)variables.

3. Results

3.1. Baseline characteristics of study population

Our study included 106 antipsychotic-naïve or minimally treated first-episode schizophrenia spectrum disorder patients (77 males, 29 females; mean age = 24.2 years). In total, 79 patients had a DSM-IV diagnosis of schizophrenia, while 26 patients were diagnosed with schizophreniform disorder, and one patient with schizoaffective disorder. Forty-one (39%) patients had a family history of schizophrenia. Mean duration of untreated psychosis (DUP) for the total sample was 34 weeks. Our sample consisted of self-reported Mixed Ancestry (n = 81, 76%), as well as Caucasian (n = 15, 14%) and Black African (n = 10, 9%) patients. The distribution of male to female patients was representative of that observed in our larger study sample (Chiliza et al., 2015) and reflects the sex distribution of patients presenting to the health care services in our catchment area. The 2-weeklymean modal dose of depot flupenthixol decanoate was 10 mg in the majority (n = 67; 63%) of patients, 15 mg in 15 (14%) patients, 20 mg in 12 (11%) patients, 5 mg in five (5%)patients, and 20 mg in one (1%) patient. In addition, 29 (27%) patients used benzodiazepines and three (3%) propranolol as needed over the course of the study, while 17 (16%) were prescribed anticholinergic drugs, and nine (8%) antidepressants. In total, 22 (21%) patients received antidepressant and/or anticholinergic co-medication, which were considered of interest as a treatment-related confounder due to their known association with weight gain and associated metabolic syndrome changes. A total of 64 (60%) patients completed the month 12 assessment; 98 (92%) patients had a treatment period of at least six months necessary to assess symptomatic remission status according to the RSWG criteria, with 63 (64%) attaining symptomatic remission.

A comparison of the baseline and end-point values for clinical and metabolic parameters is presented in Table 1. There was a significant decrease in PANSS total score as well as all factor-derived domains (i.e. positive, negative, disorganized, depressive-anxiety and excitement-hostility symptoms) from baseline to end-point (all $p < 0.001$). Mean BMI ($p < 0.001$) and triglycerides ($p < 0.001$) significantly increased, while HDL cholesterol significantly decreased ($p = 0.001$) from baseline to end-point. SBP, DBP and glucose did not change significantly from baseline to end-point. Visit-wise changes in BMI over the course of antipsychotic treatment in relation age, sex and end-point

Table 1
Comparison of baseline and end-point scores for clinical and metabolic characteristics of total study group.

Characteristic	Baseline scores Mean (SD)	End-point scores Mean (SD)	Unadjusted p-value
Clinical			
PANSS total score	94.64 (15.90)	48.16 (13.48)	<0.001
PANSS positive symptoms	17.36 (3.26)	6.06 (3.10)	<0.001
PANSS negative symptoms	20.14 (5.41)	11.52 (4.62)	<0.001
PANSS disorganized symptoms	11.98 (2.90)	6.48 (2.39)	<0.001
PANSS depressive-Anxiety symptoms	9.08 (4.25)	5.39 (2.48)	<0.001
PANSS excitement-hostility symptoms	8.29 (3.84)	4.71 (1.64)	<0.001
Metabolic			
Body mass index (kg/m2)	21.68 (3.87)	24.38 (4.97)	<0.001
Systolic BP (mmHg)	121.19 (13.66)	123.24 (12.49)	0.256
Diastolic BP (mmHg)	79.54 (10.34)	79.91 (10.18)	0.794
Glucose (mmol/L)	4.78 (0.71)	4.97 (1.37)	0.205
HDL cholesterol (mmol/L)	1.17 (0.55)	0.98 (0.26)	0.001
Triglycerides (mmol/L)	0.88 (0.52)	1.22 (0.85)	<0.001

PANSS = Positive and Negative Symptom Scale; BP = blood pressure; HDL = high-density lipoprotein.

flupenthixol dose were previously described in our study cohort (see Chiliza et al., 2015).

3.2. Relationship between weight loss and psychopathology change scores

A total of 20 (19%) patients lost weight over the course of our study; no significant differences in clinical change scores were noted between this subgroup and the rest of the study population ($p > 0.05$).

3.3. Relationship between metabolic change scores and treatment characteristics

DUP, modal antipsychotic dose and treatment duration were not significantly associated with any of the metabolic change scores of interest ($p > 0.05$). Weight gain and associated metabolic change scores were compared between remitters ($n = 63$) and non-remitters ($n = 35$) in a subgroup of 98 patients for whom sustained symptomatic remission could be assessed. No significant differences in change scores for BMI, SBP, DBP, glucose, triglycerides or HDL cholesterol were noted between remitters and non-remitters.

3.4. Correlation between baseline psychopathology and metabolic characteristics

In the total study group, triglyceride levels were negatively correlated with disorganized symptom severity at baseline ($r = -0.29$, $p = 0.002$). This correlation retained significance following post-hoc Bonferroni correction (0.008). A trend was also noted for an inverse association between triglycerides and total PANSS score at baseline ($r = -0.16$, $p = 0.065$). BMI, glucose and HDL cholesterol were not significantly correlated with total PANSS score or any specific symptom domain at baseline (Table 2).

3.5. Correlations between psychopathology improvement and metabolic change scores

BMI change scores were inversely correlated with change in PANSS total ($r = -0.25$; $p = 0.011$) as well as positive ($r = -0.23$; $p = 0.019$), depressive-anxiety ($r = -0.21$; $p = 0.031$) and disorganized symptoms ($r = -0.32$; $p < 0.001$) but not negative or excitement-hostility symptoms ($p > 0.05$). The inverse correlation between BMI and disorganized symptom change scores (Fig. 1) survived Bonferroni correction (0.008). Change in fasting glucose was inversely correlated with change in positive symptoms ($r = -0.21$; $p = 0.034$), while change in triglycerides was inversely associated with change in disorganized symptoms ($r = -0.20$; $p = 0.040$). SBP, DBP and HDL change scores were not significantly related to improvement in global psychopathology or factor-derived symptom domains (Table 3).

3.6. Metabolic factors as predictors of psychopathology improvement

Separate linear regression models were constructed with change scores for global psychopathology (model 1) and the domains of disorganized (model 2), positive (model 3) and depressive-anxiety (model 4) symptoms as dependent variables, selected based on their significant correlations with metabolic parameter change scores on initial analysis. We entered BMI and metabolic change scores as predictors and socio-demographic (age, sex, ethnicity), clinical (substance use) as well as treatment-related (antipsychotic dose, treatment duration, co-medication with antidepressants and/or anticholinergics) factors as covariates. In model 1 ($R^2 = 0.26$, $F(14,89) = 2.29$, $p = 0.010$), BMI change scores ($\beta = -1.25$, $p = 0.061$) and treatment duration ($\beta = -0.72$, $p < 0.001$) were independent predictors of the variance in PANSS total symptoms. In model 2 ($R^2 = 0.28$, $F(14,89) = 2.50$, $p = 0.005$), BMI change scores ($\beta = -0.29$, $p = 0.004$) and treatment duration ($\beta = -0.09$, $p = 0.002$) were also significant predictors of the variance in PANSS disorganized symptoms. In model 3, ($R^2 = 0.30$, $F(14,89) = 2.73$, $p = 0.002$), only treatment duration ($\beta = -0.16$, $p < 0.001$) was a significant predictor of the variance in positive symptoms. Model 4 was not significant for improvement in depressive-anxiety symptoms ($R^2 = 0.17$, $F(14,89) = 1.27$, $p = 0.241$).

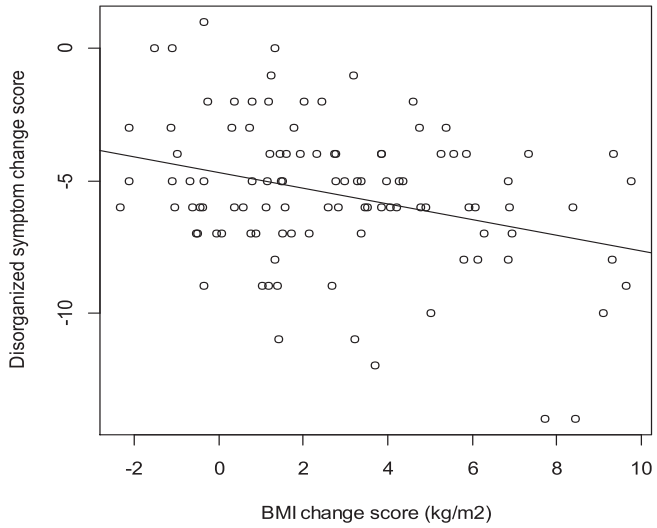

Fig. 1. Scatterplot diagram illustrating a significant inverse association between change scores for body mass index (BMI) and the disorganized symptom domain.

4. Discussion

The main finding from the present study was that increased BMI significantly correlated with improved global psychopathology and the disorganized symptoms of schizophrenia over the first 12 months of antipsychotic treatment. This association remained significant after controlling for the effects of age, sex, ethnicity, substance use, co-medication with antidepressants and/or anticholinergics, as well as the dose and duration of antipsychotic exposure. These findings are in accordance with those reported in previous studies suggesting a link

Table 2
Results from correlation analysis evaluating the linear relationship between clinical symptoms and metabolic parameters at baseline, presented as the R-value and corresponding unadjusted p-values.

	PANSS total baseline	Positive baseline	Negative baseline	Disorganized baseline	Depressive-anxiety baseline	Excitement-hostility baseline
BMI (kg/m2) baseline	−0.11; 0.265	0.04; 0.650	−0.07; 0.487	−0.12; 0.219	−0.05; 0.646	−0.03; 0.778
SBP (mmHg) baseline	−0.04; 0.659	−0.10; 0.305	0.04; 0.661	0.06; 0.565	−0.07; 0.474	−0.11; 0.253
DBP (mmHg) baseline	−0.04; 0.685	−0.04; 0.719	0.07; 0.464	−0.09; 0.381	0.04; 0.713	−0.10; 0.291
Glucose (mmol/L) baseline	−0.04; 0.648	0.01; 0.916	−0.02; 0.869	−0.13; 0.182	−0.08; 0.410	0.05; 0.609
HDL cholesterol (mmol/L) baseline	−0.01; 0.936	0.05; 0.633	0.06; 0.523	−0.06; 0.565	0.04; 0.710	−0.14; 0.157
Triglycerides (mmol/L) baseline	−0.16, 0.065	−0.01; 0.912	−0.14; 0.153	−0.29; 0.002	0.01; 0.903	−0.09; 0.375

PANSS = Positive and Negative Symptom Scale; BP = blood pressure; HDL = high-density lipoprotein.

Table 3
Results from correlation analysis evaluating the linear relationship between clinical and metabolic change scores, presented as the R-value and corresponding unadjusted p-values.

	PANSS total change	Positive change	Negative change	Disorganized change	Depressive-anxiety change	Excitement-hostility change
BMI (kg/m2) change	−0,25; 0.011	−0.23; 0.019	−0.09; 0.364	−0.32; <0.001	−0.21; 0.031	−0.02; 0.866
SBP (mmHg) change	0.06; 0.524	<−0.01; 0.973	0.07; 0.507	0.05; 0.594	0.06; 0.538	−0.02; 0.868
DBP (mmHg) change	<−0.01; 0.925	<0.01; 0.926	0.06; 0.570	0.01; 0.934	0.06; 0.539	−0.12; 0.240
Glucose (mmol/L) change	−0.06; 0.513	−0.21; 0.034	0.11; 0.256	−0.01; 0.935	0.02; 0.874	−0.04; 0.717
HDL cholesterol (mmol/L) change	<0.01; 0.978	0.10; 0.308	0.02; 0.832	−0.04; 0.674	−0.06; 0.509	−0.11; 0.268
Triglycerides (mmol/L) change	−0.09; 0.341	−0.13; 0.168	−0.13; 0.176	−0.20; 0.040	0.02; 0.846	0.06; 0.550

PANSS = Positive and Negative Symptom Scale; BP = blood pressure; HDL = high-density lipoprotein.

between treatment-emergent weight gain and therapeutic response in schizophrenia spectrum disorder patients (Sharma et al., 2014; Raben et al., 2018).

Importantly, our results extend previous research insofar as we were able to exclude several important factors that may have confounded these findings. First, we were able to control precisely for dose and duration of antipsychotic exposure. Similarly, poor adherence is likely associated with both worse outcome and reduced obesogenic effect of antipsychotics. Our use of depot formulation antipsychotic provided assured delivery and removed the confounding effect of non-adherence. This may be important, given the very high rates non- and partial adherence reported in the early stages of illness (Coldham et al., 2002). Additionally, by including only first-episode and minimally treated or never treated patients, we removed the effects of illness chronicity and previous medication. Finally, by standardising treatment with a single antipsychotic we addressed the potential confound of differential treatment effects in terms of both efficacy and weight gain. To the best of our knowledge, this is the first study to report an independent effect of weight gain on improvement in disorganized symptoms in a sample treatment-naïve or minimally treated patients with schizophrenia spectrum disorder. Most previous studies reporting a relationship between metabolic side effects and clinical improvement were conducted in chronic samples. Also, most studies investigated patients treated with clozapine and olanzapine - the two antipsychotics associated with the greatest risk of weight gain - with other drugs being poorly represented (Sharma et al., 2014).

Our results suggest that the relationship is not restricted to these two drugs, and may be present even with antipsychotics less frequently associated with weight gain. Indeed, flupenthixol is considered to be relatively "weight neutral" (Messer et al., 2009), although first-episode patients are more susceptible and significant weight gain has been reported in these patients (Chiliza et al., 2015). Whether weight gain is a necessary concomitant of efficacy (Sharma et al., 2014) remains to be further elucidated, although our results suggest that this is not the case, as the 20 patients who lost weight in our study did not do significantly worse than the rest of the sample.

There are several possible explanations for the link between weight gain and favourable treatment response. Firstly, it may be that greater improvement in symptoms leads to better and more structured health-seeking behaviours, including proper self-care and healthier diet. In this respect, our finding of an association between weight gain and improvement in disorganized symptoms specifically, may be relevant. Disorganized symptoms are a major contributor to acute impairment in functioning (Ortiz et al., 2017), health and wellbeing (Javitt, 2015). A second possibility is that the effects of antipsychotics on neurotransmitters that are responsible for weight gain may, at least in part, also be responsible for the efficacy of these agents (Meltzer et al., 2003). In particular, serotonin signalling may play a role, given its involvement in the regulation of appetite and satiety, with 5HT2C receptor blockade being directly implicated in antipsychotic-associated weight gain (Reynolds et al., 2006; Panariello et al., 2011), as well as its association with clinical response in schizophrenia (Gressier et al., 2016). Unlike most conventional antipsychotics, flupenthixol is a 5HT2A and 5HT2C receptor blocker (Wiesbeck et al., 2003). The role of the orexin hypothalamic neuropeptides may also be relevant. Orexins play a role in appetite regulation and energy homeostasis (Panariello et al., 2011) and share interaction mechanisms with serotonin (Donovan and Tecott, 2013). In this context, and of relevance to our findings, Chien et al. (2015) recently reported a correlation between lower disorganized and negative symptom severity and higher orexin A levels in a study of 127 schizophrenia patients, implicating orexin in treatment response.

Several recent studies have reported that elevated lipids may predict clinical response in schizophrenia (Solberg et al., 2015, 2016). Our results in this regard were less clear-cut. Thus, while we found several significant correlations between treatment-emergent metabolic changes other than weight gain and a decrease in specific factor-derived domain scores in the bivariate correlational analyses, none of these associations remained significant in the regression models. Nevertheless, our finding of an association between baseline triglycerides and PANSS total symptom severity, and increased triglycerides and greater reductions in disorganized symptoms, is consistent with previous work reporting an association between elevated triglycerides and fewer negative symptoms (Procyshyn et al., 2007; Lally et al., 2013), which share a strong association with disorganized symptoms (Demjaha et al., 2012). An association between increased lipids and better treatment response could be explained by lipid partitioning and altered blood-brain barrier permeability affecting antipsychotic levels, although elevated triglycerides may also exert a favourable effect on central serotonin transmission (Dursun et al., 1999) and perhaps also reflect a favourable change in central lipid metabolism and myelination potential or efficacy (Chrast et al., 2011). Finally, the inverse correlation between glucose and positive symptom change scores that we found is consistent with the proposal that insulin signalling is the common pathway linking metabolic risk with therapeutic benefit (Girgis et al., 2008).

The strengths of this study lie in its longitudinal design and evaluation of a well-characterized cohort of first-episode, minimally treated patients. Also, regular clinical and laboratory assessments allowed for accurate evaluation of changes over time. In addition, standardised treatment with a single antipsychotic ruled out the differential effects of treatment. However, there are important limitations. First, a longer treatment period would have been preferable and may have more clearly identified relationships between lipid and glucose changes and treatment outcome. Second, our sample was drawn from a largely socio-economically deprived community with low baseline BMI. Thirdly, our study did not include the assessment of waist circumference as an indicator of central obesity, and dietary habits and physical activity as determinants of cardio-metabolic risk in schizophrenia spectrum disorder patients treated with antipsychotics were not examined. Finally, our study only included patients treated with flupenthixol decanoate. These limitations mean that our findings are not necessarily generalizable to other patient populations which may differ in terms of clinical profile, treatment approach and metabolic risk profile.

In conclusion, our study supports the notion that weight gain is related to antipsychotic efficacy, perhaps via shared mechanistic pathways. The possible clinical usefulness of assessment and monitoring of metabolic syndrome risk in predicting treatment outcome remains to be defined.

Conflict of interest statement

HL, LP, FS, LA and SK report no conflicts of interest. BC has received honoraria from Lundbeck, Mylan and Sandoz for speaking at educational meetings. RE has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck.

Contributors

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CHAPTER THREE

Relationship between changes in metabolic syndrome constituent components over 12 months of treatment and cognitive performance in first-episode schizophrenia

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ORIGINAL ARTICLE

Relationship between changes in metabolic syndrome constituent components over 12 months of treatment and cognitive performance in first-episode schizophrenia

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Abstract

Few studies have investigated the longitudinal effects of treatment-emergent metabolic syndrome changes on cognitive performance in first-episode psychosis. The aim of the present study was to determine the associations between changes in metabolic syndrome constituent component over 12 months of treatment and end-point cognitive performance in schizophrenia spectrum disorders. This single site-cohort study included 72 minimally treated or antipsychotic-naïve first-episode patients. Cognitive performance was evaluated using the MATRICS Consensus Cognitive Battery (MCCB). Our primary objective of interest was the relationship between metabolic syndrome constituent component changes over 12 months of treatment and end-point cognitive performance. Secondary objectives included investigating whether this relationship was affected by age, sex, antipsychotic dose, treatment duration and substance use. Weight gain predicted better overall cognition ($p = 0.02$) at end-point, adjusting for age, sex, substance use, baseline cognitive score and BMI, modal antipsychotic dose and treatment duration. Weight loss ($p = 0.04$) and substance use ($p = 0.01$) were both associated with poorer working memory performance at end-point. Low baseline BMI showed differential effects on end-point working memory performance in substance users (unfavorable) compared to non-users (favorable) ($p < 0.05$). In conclusion, weight gain over the course of antipsychotic treatment is associated with better overall cognitive performance and the working memory domain in first-episode schizophrenia spectrum disorder patients. In contrast, low baseline BMI may represent an unfavorable marker in substance users, who demonstrated weight loss compared to non-users.

Keywords First-episode schizophrenia spectrum disorders · Cognitive performance · Working memory · MCCB · Weight gain

Introduction

In patients with schizophrenia, metabolic syndrome is associated with cognitive impairments, including executive dysfunction, poor working memory and altered attention/vigilance (Guo et al. 2013; Bora 2016). This is important, given the increased risk for development of metabolic syndrome in schizophrenia patients (Mitchell et al. 2013).The impact of metabolic syndrome on cognitive dysfunction is pronounced in patients with severe negative symptoms, and increases in parallel with the number of metabolic syndrome risk factors present (Lindenmayer et al. 2012; Boyer et al. 2013; Botis et al. 2016; Bora et al. 2017a). Meta-analyses have further confirmed the effects of metabolic syndrome and type II diabetes mellitus (DM II) as determinants of poor overall cognition in schizophrenia (Bora et al. 2017b). Better cognitive performance at baseline has also been associated with a favorable metabolic profile at follow-up in schizophrenia (Storch-Jakobsen et al. 2018).

Individual metabolic syndrome constituent components may exert distinct effects on specific cognitive domains in schizophrenia. For example, elevated waist circumference

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has been correlated with decreased motor speed (Botis et al. 2016) and attention/vigilance (Lindenmayer et al. 2012), while hypertension and elevated triglycerides have been associated with poorer verbal memory (Friedman et al. 2010; Goughari et al. 2015). On the other hand, opposing literature suggests certain metabolic syndrome features such as hypertension, hyperglycemia and dyslipidaemia may be associated with better performance in certain cognitive domains affected in schizophrenia (Goughari et al. 2015; Wysokinski et al. 2013). Interestingly, several prospective studies have reported that changes in certain metabolic syndrome constituent components including elevated lipids predict cognitive improvement in schizophrenia (Krakowski and Czobor 2011; Nasrallah and Blom 2015). These findings are in keeping with studies showing an association between high cholesterol levels and better performance on verbal fluency, reasoning, motor speed and attention/concentration in population-based cohorts (Elias et al. 2005).

In contrast to a well-documented association with psychopathology improvement in schizophrenia (Raben et al. 2018), the relationship between weight gain and cognitive performance over the course of antipsychotic exposure remains poorly described. Indeed, there is a paucity of evidence from longitudinal studies of well-characterized first-episode patients investigating the relationship between changes in antipsychotic-induced metabolic syndrome constituent components and cognitive performance in schizophrenia. In response to this knowledge gap, the aim of the present study was to determine the associations between changes in metabolic syndrome constituent component over 12 months of treatment and end-point cognitive performance in schizophrenia spectrum disorders. Our primary objective was to investigate the relationship between change in body mass index (BMI) over 12 months of treatment and end-point cognitive performance. Secondary objectives included to determine whether this relationship is affected by age, sex, antipsychotic dose, treatment duration and substance use.

Firstly, we hypothesized that increased BMI would be associated with better overall cognition at end-point, adjusting for modal antipsychotic dose, treatment duration and substance use, in accordance with our previous finding that weight gain predicted global psychopathology improvement in first-episode patients independent of these covariates (Luckhoff et al. 2018). Secondly, we anticipated that substance use would affect the relationship between weight gain and end-point performance in specific cognitive domains, given our previous finding that patients who used cannabis, unlike their non-using counterparts, did not gain significant weight when treated with antipsychotics (Scheffler et al. 2018). In addition, our focus on working memory in particular was motivated by its importance in the control of appetite and weight gain (Higgs and Spetter 2018) as well as recent evidence that ongoing substance use is associated with poorer working memory performance in first-episode or early psychosis (Bogaty et al. 2018; Sanchez-Gutierrez et al. 2018).

Materials and methods

Study design and ethics approval

The present single-site longitudinal study, which recruited minimally treated or antipsychotic-naive first-episode schizophrenia patients, was conducted as part of a larger parent project (N06/08/148), with ethical approval obtained from the Health and Research Ethics Committee (HREC) at Stellenbosch University (SU). Written, informed consent was obtained from all participants, and in the case of participants younger than 18 years of age, we obtained written, informed consent from parents or legal guardians.

Selection of study participants

Study participants were selected from first admissions to hospitals and community clinics in the metro and rural areas of North Eastern Cape Town, the Winelands and West Coast over a 4 year period (2007–2011). Inclusion criteria were men and women, in- or outpatients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria included lifetime exposure to more than 4 weeks of antipsychotic medication, serious or unstable medical condition, and substance-induced psychosis.

Antipsychotic treatment

Patients were treated according to a fixed protocol with flupenthixol decanoate, a depot antipsychotic. There was a lead-in period of 7 days with oral flupenthixol 1–3 mg/day followed by flexible doses of flupenthixol decanoate intramuscular injections 2-weekly. Permitted concomitant medications included lorazepam, anticholinergics, propranolol, antidepressants and medications for medical conditions. Prohibited medications included other antipsychotics, mood stabilizers and psychostimulants.

Patient assessments

Clinical assessments

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1994). The MATRICS Consensus Cognitive Battery (MCCB) was utilized as a tool specifically designed and validated for the assessment of

cognitive functioning in schizophrenia (Nuechterlein and Green 2006). The MCCB comprises seven domains and a composite score. The individual domains are: 1) speed of processing, 2) attention/vigilance, 3) working memory, 4) verbal learning, 5) visual learning, 6) reasoning and problem solving, and 7) social cognition. The MCCB was administered at baseline, month 6 and month 12 by trained psychologists under supervision of an experienced clinical psychologist and psychiatrist. The MCCB computer program was used to transform raw scores into individual domain and composite T-scores. Age- and sex-corrected norms were used according to the guidelines outlined in the MCCB manual (Nuechterlein and Green 2006). We compared metabolic syndrome constituent component change scores with MCCB end-point scores rather than the MCCB change scores, as the baseline cognitive tests were performed while patients were acutely psychotic and this may have confounded the scores. The end-point MCCB scores therefore assessed cognitive performance in clinically stable patients.

Metabolic assessments

A physical examination was performed at baseline, follow-up and study completion. Body weight was measured at baseline and months 3, 6, 9 and 12. Study participants removed all surplus clothing including socks and shoes and were weighed on an electronic scale calibrated throughout the study. Height was measured using a pre-fixed wall-mounted measuring tape.BMI was also calculated as the patient's body weight in kilograms (kg) divided by their height in meters squared (m^2). Clinically significant weight gain was defined as >7% increase in body weight from baseline to end-point (McIntyre et al. 2003). A peripheral venous blood sample was collected from participants following an 8 hour fasting period and 10 minute rest prior to venepuncture. Biochemical testing was performed at baseline and again at months 3, 6, 9 and 12, and included assessment of the fasting lipid profile (triglycerides, total, LDL and HDL cholesterol) and glucose levels.

Urine toxicology

Urine toxicology was performed at baseline and again at months 3, 6 and 12 to assess use of cannabis, methaqualone and methamphetamine over the course of the study. Patients who tested positive were classified as substance use positive.

Statistical analysis

Statistical analyses were performed using the R Studio software package (version 3.2.4) and confirmed by a biostatistician using the IBM SPSS software program (version 25). All participants with at least one baseline and one follow-up measure were included for analysis. End-point scores were calculated by last observation carried forward, and metabolic change scores were calculated by subtracting the baseline score from the end-point score. Categorical characteristics were described using cross-tabulation and frequency tables and compared between study groups using the Pearson's Chi-Squared or Fisher's exact tests. For normally distributed data, quantitative phenotypes are given as means and the standard deviation (SD). Linear correlations between metabolic change scores and MCCB end-point scores were described using Pearson's correlation analysis. Winsorized data were utilized for triglyceride and HDL cholesterol change scores in order to minimize the potential effects of outliers, and a significance level of $p < 0.10$ was used to identify predictor variables for subsequent linear regression analyses. In all other analyses, statistical significance was defined as a p value <0.05.

Results

Characteristics of study population

From an initial group of 126 patients, we included 72 largely treatment-naive, first-episode schizophrenia spectrum disorder patients (53 males, 19 females; mean age = 24.2 years) for whom sufficient data were available to calculate metabolic syndrome constituent component change scores (baseline and at least one follow-up visit) as well as composite MCCB score at end-point. In total, 57 patients (79%) had a DSM-IV diagnosis of schizophrenia, while 15 patients (21%) were diagnosed with schizophreniform disorder. The sample consisted mostly ($n = 53$; 74%) of patients of Mixed Ancestry, and further included 11 Caucasian (15%) and eight Black African (11%) patients. The majority of males tested positive for use of illicit substances ($n = 31$, 58%) compared to a minority ($n = 4$, 21%) of females. In total, 35 patients (49%) tested positive for substance use, of which 28 (80%) were positive for cannabis use. Modal 2-weekly dose of depot flupenthixol decanoate was 10 mg in 47 (65%) patients, 15 mg in 15 (21%) patients, 20 mg in seven (10%) patients, and 5 mg in three (4%) patients.

The baseline and end-point scores for the cognitive and metabolic outcomes of interest are presented and compared in Table 1. There was a significant increase in MCCB composite score ($p = 0.04$) as well as the attention/vigilance ($p < 0.01$) and reasoning/problem-solving domains ($p = 0.01$) from baseline to end-point. In addition, a significant increase in mean BMI ($p < 0.01$) and triglycerides ($p < 0.01$) as well as a decrease in HDL cholesterol ($p < 0.01$) was noted from baseline to end-point. Glucose ($p = 0.18$), total cholesterol ($p = 0.39$) and LDL cholesterol ($p = 0.30$) did not change significantly over the course of the study.

Table 1 Comparison of baseline and end-point scores for cognitive performance and metabolic status for total study group, provided along with corresponding unadjusted *p* values

Cognitive and metabolic characteristics	Baseline scores Mean (SD)	End-point scores Mean (SD)	Comparison baseline to end-point (unadjusted *P* value)
MCCB Composite score	21.06 (13.33)	26.40 (14.43)	0.04**
MCCB Working memory	27.91 (12.40)	31.51 (12.34)	0.11
MCCB Speed of processing	23.22 (11.11)	27.27 (13.20)	0.07
MCCB Reasoning/problem solving	32.81 (9.25)	37.40 (10.41)	<0.01**
MCCB Attention/vigilance	24.64 (11.64)	31.86 (9.93)	<0.01**
MCCB Visual learning	31.96 (13.51)	36.49 (12.90)	0.06
MCCB Verbal learning	33.61 (8.52)	34.36 (7.78)	0.61
MCCB Social cognition	46.25 (15.22)	49.57 (18.96)	0.28
Body mass index (kg/m^2)	21.72 (4.18)	24.66 (5.36)	<0.01**
Glucose (mmol/L)	4.81 (0.76)	5.10 (1.61)	0.18
HDL cholesterol (mmol/L)	1.16 (0.51)	0.96 (0.25)	<0.01**
Triglycerides (mmol/L)	0.85 (0.41)	1.22 (0.84)	<0.01**
Total cholesterol (mmol/L)	4.22 (1.06)	4.36 (0.87)	0.39
LDL cholesterol (mmol/L)	2.71 (0.89)	2.85 (0.82)	0.30

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *MCCB* MATRICS Consensus Cognitive Battery, ** statistically significant

Effects of baseline BMI and weight change on end-point cognitive scores

Baseline BMI was not associated with the composite MCCB score or any specific cognitive domains at end-point ($p > 0.05$). A total of 45 patients (63%) experienced clinically significant weight gain, which was not significantly associated with the composite MCCB end-point score or any of the specific cognitive domains at end-point ($p > 0.05$). In total, 14 patients (19%) lost weight over the course of the present study. These patients had poorer end-point working memory scores (mean = 25.43) compared to the rest of the patient group (mean = 32.98) ($p = 0.04$). Weight loss was not significantly associated with poorer cognitive performance at end-point for the composite MCCB score or other specific domains ($p > 0.05$).

Correlations between metabolic syndrome change scores and end-point cognitive scores

Pearson correlation coefficients were calculated to assess the linear relationship between 1) the composite MCCB score/specific cognitive domains at end-point, and 2) metabolic change scores where a significant increase (i.e. BMI, triglycerides) or decrease (i.e. HDL cholesterol) was noted from baseline to end-point, as shown in Table 2. BMI change scores were significantly positively correlated with the MCCB working memory domain at end-point ($r = 0.28$; $p = 0.02$). A similar trend was noted towards a positive association between BMI change scores and the composite MCCB score at end-point ($r = 0.20$, $p = 0.09$). In addition, HDL change scores were inversely associated with the reasoning/problem solving domain ($r = -0.23$; $p = 0.05$) at end-point, although this

Table 2 Results from correlation analysis evaluating the linear relationship between metabolic change scores and MCCB composite score and specific cognitive domains at end-point, presented as the Rho-value and corresponding unadjusted *p* values

	Composite MCCB end-point score	WM end-point score	SOP end-point score	RPS end-point score	AV end-point score	VISL end-point score	VERBL end-point score	SC end-point score
BMI change score (kg/m2)	0.20; 0.09	0.28; 0.02	0.19; 0.12	0.02; 0.89	0.07; 0.56	0.10; 0.40	0.16; 0.19	0.17; 0.16
HDL cholesterol change score (mmol/L)	−0.19; 0.12	−0.15; 0.22	−0.14; 0.25	−0.23; 0.05	−0.07; 0.53	−0.07; 0.57	−0.19; 0.10	−0.14; 0.25
Triglycerides change score (mmol/L)	0.08; 0.52	0.02; 0.86	−0.02; 0.86	0.07; 0.54	−0.03; 0.81	0.12; 0.31	0.05; 0.69	0.12; 0.31

Predictor variables were identified using a significance level of $p < 0.10$

AV attention/vigilance, *BMI* body mass index, *HDL* high-density lipoprotein, *MCCB* MATRICS Consensus Cognitive Battery, *RPS* reasoning/problem solving, *SC* social cognition, *SOP* speed of processing, *VERBL* verbal learning, *VISL* visual learning, *WM* working memory

correlation did not remain significant when outliers ($n = 3$) were removed ($r = -0.12$, $p = 0.33$). Based on results from initial exploratory correlation analyses, we therefore identified the composite MCCB end-point and working memory domain as our dependent variables of interest, and the BMI change score as our metabolic predictor of interest.

Linear regression analyses

Linear regression models were constructed to assess the relationship between BMI change scores and the composite MCCB score as well as working memory domain at end-point, incorporating clinical (age, sex, substance use, baseline cognitive score and BMI) and treatment-related (modal antipsychotic dose, treatment duration) factors as covariates (Table 3). Increase in BMI ($\beta = 1.17$, $p = 0.02$) significantly predicted a higher composite MCCB score at end-point, adjusting for age, sex, substance use, modal antipsychotic dose, treatment duration, baseline composite score and BMI as covariates. In addition, weight gain ($\beta = 0.89$, $p = 0.02$) predicted better working memory performance at end-point, adjusting for age, sex, modal antipsychotic dose, treatment duration, baseline composite score and BMI as covariates (Table 3). The effect of increased BMI as a predictor of end-point working memory performance was however non-significant ($\beta = 0.63$, $p = 0.13$) when substance use was also incorporated into a linear model ($R^2 = .58$, $F(8,46) = 8.24$, $p < 0.01$) adjusting for the same covariates (i.e. age, sex, modal antipsychotic dose, treatment duration, baseline composite score and BMI). We therefore performed subsequent sub-analyses to further explore the effects of substance use on inter-relationship between baseline BMI, weight gain and end-point working memory performance.

Effects of substance use on baseline BMI, weight change and working memory performance

Substance use was associated with poorer working memory scores at end-point ($p = 0.01$), with a significant improvement in performance from baseline to end-point only evident for non-users ($p = 0.02$). In addition, the majority ($n = 11$; 78%) of patients who lost weight ($n = 14$), which was itself associated with lower end-point working memory scores ($p = 0.04$), tested positive for substance use over the course of the study. Moreover, a significant increase in BMI over the course of the study was evident for non-users ($p < 0.01$) but not substance users ($p > 0.05$). Baseline BMI was also significantly lower in substance users compared to non-users ($p = 0.03$). Lastly, low baseline BMI ($\beta = -0.86$, $p = 0.01$) predicted better end-point

Table 3 Linear regression models incorporating clinical, metabolic and treatment-related factors as predictors of MCCB composite score and the working memory domain at end-point

MCCB composite end-point score							
					Predictors		
	R-squared	Model df	*F*-statistic	*P* value	Beta-coefficient	*T*-value	*P* value
	0.58	8,41	9.53	<0.01			
BMI change score					1.17	2.38	0.02**
Age					0.25	1.06	0.30
Sex					−3.00	−1.04	0.31
Modal antipsychotic dose					−0.04	−0.10	0.92
Treatment weeks					−0.03	−0.19	0.85
Substance use					1.27	0.41	0.69
Baseline MCCB composite score					0.70	6.75	<0.01**
Baseline BMI					−0.58	−1.67	0.10
MCCB working memory end-point score							
					Predictors		
	R-squared	Model df	*F*-statistic	*P* value	Beta-coefficient	*T*-value	*P* value
	0.49	7,47	8,37	<0.01			
BMI change score					0.89	2.40	0.02**
Age					−0.03	−0.15	0.88
Sex					0.04	0.02	0.99
Modal antipsychotic dose					0.45	1.31	0.20
Treatment weeks					0.05	0.32	0.75
Baseline MMCCB working memory					0.57	6.46	<0.01**
Baseline BMI					−0.43	−1.49	0.14

BMI Body mass index, *MCCB* MATRICS Consensus Cognitive Battery, ** statistically significant

working memory performance in non-users, adjusting for age, sex, modal antipsychotic dose, treatment duration and baseline cognitive score ($R^2 = .55$, $F(6,25) = 7.35$ $p < 0.01$). In contrast, low baseline BMI predicted poorer working memory at end-point in substance users ($\beta = 1.22$, $p = 0.04$) adjusting for the same covariates ($R^2 = .55$, $F(6,17) = 4.66$, $p < 0.01$).

Discussion

The main finding from this study was that increased BMI over 12 months of treatment predicted better overall cognition and working memory performance in antipsychotic-naïve or minimally treated first episode schizophrenia spectrum disorder patients, independent of the degree of antipsychotic exposure. In contrast, substance use and weight loss were both associated with lower end-point working memory scores. Our findings are in agreement with those from previous studies demonstrating an association between weight gain and symptomatic improvement in schizophrenia (Raben et al. 2018). In addition, they expand on previous research by suggesting that an increase in BMI over the course of antipsychotic treatment is associated with favorable overall cognitive outcome and better working memory performance.

There are several possible explanations for the association between weight gain and better cognitive performance at end-point evident from our study. Firstly, changes in serotonin signaling may be involved, with 5HT receptor blockade being implicated in antipsychotic-induced weight gain (Panariello et al. 2011) and improvement in cognitive performance (Schmitt et al. 2006). In contrast, aberrant 5HT transmission has been implicated in poor cognitive functioning in animal and human studies (Strac et al. 2016) with 5HT receptor agonists known to not only impair working memory performance (Luciana et al. 1998), but also decrease appetite and promote weight loss (Halford et al. 2011). In this context, flupenthixol is known to exhibit 5HT receptor blockade (Wiesbeck et al. 2003) which may underscore its effects on both weight gain (Chiliza et al. 2015) and cognitive improvement (Olivier et al. 2015) previously demonstrated in our larger study cohort. Secondly, glucose metabolism and altered insulin signaling have been proposed as common mechanisms underscoring the effects of weight gain on symptomatic improvement in schizophrenia (Girgis et al. 2008). Weight gain is known to increase levels of insulin, the acute administration of which has been shown to improve cognitive performance (Shemesh et al. 2012). Similarly, acute administration of glucose improves memory in schizophrenia patients (Newcomer et al. 1999). Indeed, insulin plays a key role in modulating the level and activity of neurotransmitters including serotonin in brain regions such as the hippocampus and hypothalamus (Umbriaco et al. 1995; Orosco et al. 2000; Dickinson and Harvey 2009). Important metabolic changes considered deleterious in chronic schizophrenia may therefore be considered favorable in antipsychotic-naïve patients in the acute stage of treatment.

In the present study, weight loss and substance use were both associated with poorer working memory at end-point, with the majority of patients who lost weight testing positive for substance over the course of treatment. It remains unclear whether weight loss is associated with worsening of psychopathology symptoms in schizophrenia (Chukhin et al. 2016), and most studies have shown that weight loss has a beneficial effect on cognition in obese individuals (Smith et al. 2010). Therefore, the influence of weight loss evident in our study may rather reflect the effects of substance use on working memory performance. Interestingly, multiple studies have shown that cannabis use in particular is associated with better working memory performance in first-episode psychosis patients, as demonstrated in a meta-analysis by Yücel et al. (2012). However, a meta-analysis by Sanchez-Gutierrez and colleagues (Sanchez-Gutierrez et al. 2018) concluded that ongoing cannabis use in first-episode psychosis may exert deleterious effects on cognition. In accordance with our study, findings from a recent meta-analysis of 14 studies by Bogaty et al. (2018) further suggest that comorbid cannabis use is indeed associated with poorer working memory performance in early-onset psychosis.

We further demonstrated the favorable effects of low baseline BMI as a predictor of better working memory in substance non-users, who showed a significant increase in BMI over the course of our study, as well as a significant improvement in working memory from baseline to end-point. Low baseline BMI may represent a favorable prognostic indicator in antipsychotic-naïve, substance non-using patients, who are also at greater risk for weight gain (Basson et al. 2001; Kinon et al. 2005; Raben et al. 2018). The favorable effects of a low baseline BMI in the context of weight gain is further evidenced by its association with symptomatic remission and recovery in schizophrenia (Novick et al. 2007, 2009; Stauffer et al. 2011). In contrast, baseline BMI showed the opposite effect in substance users, consistent with the observation that cannabis users did not gain significant weight over the course of treatment in our larger sample (Scheffler et al. 2018). Weight loss or failure to gain weight may therefore represent a poor prognostic marker in substance users with schizophrenia.

The present study had several important limitations, including a short study duration and relatively small sample size, which limited our ability to explore the putative moderating effect of substance use on the relationship between BMI and working memory performance. Moreover, our sample generally had a low baseline BMI, which may conceivably have influenced our results. Furthermore, our study did not include

the assessment of waist circumference as an indicator of central obesity, and dietary habits and physical activity as determinants of cardio-metabolic risk in schizophrenia spectrum disorder patients treated with antipsychotics were not examined. Also, our findings are not necessarily generalizable to other patient populations which may differ in terms of clinical profile, treatment approach and metabolic risk profile. However, the strength of the present study lies in the evaluation of a well-characterized sample of first-episode patients, with regular laboratory assessments, a mode of antipsychotic delivery that was standardized, and assured adherence.

Conclusions

In conclusion, our study demonstrated that weight gain over 12 months of treatment is associated with better overall cognition as well as working memory in first-episode schizophrenia spectrum disorder patients, independent of age, sex, and the degree of antipsychotic exposure. In addition, our findings suggest that substance use disrupts the relationship between baseline BMI, weight gain and working memory in first-episode schizophrenia spectrum disorders. Our study supports the role of weight gain as a predictor of better cognitive performance in schizophrenia. In contrast, failure to gain weight may represent an unfavorable marker for poor working memory performance in substance users.

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Compliance with ethical standards

Conflicts of interest Bonginkosi Chiliza has received honoraria from Lundbeck, Mylan and Sandoz for speaking at educational meetings. Robin Emsley has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka. Hilmar Luckhoff, Lebogang Phahladira, Freda Scheffler, Stefan du Plessis, Laila Asmal, Riaan Oosthuizen, and Sanja Kilian declare that they have no conflicts of interest.

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CHAPTER FOUR

Fronto-limbic white matter fractional anisotropy and body mass index in first-episode schizophrenia spectrum disorder patients compared to healthy controls

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Fronto-limbic white matter fractional anisotropy and body mass index in first-episode schizophrenia spectrum disorder patients compared to healthy controls

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ABSTRACT

In this diffusion tensor imaging study, we explored the associations of body mass index (BMI) with white matter microstructure in first-episode schizophrenia spectrum disorder patients (n = 69) versus healthy controls (n = 93). We focused on fractional anisotropy (FA) measures for fronto-limbic white matter tracts known to connect brain regions which form part of a "core eating network". Secondary objectives included the associations of body mass with global illness severity, psychopathology and depressive symptoms. In a multivariate analysis of covariance (MANCOVA) model, there was a significant interaction between BMI and group (patient versus control) across the fronto-limbic white matter tracts of interest ($F(1,155) = 4.91$, $p = 0.03$). In a sub-analysis, BMI was significantly inversely correlated with FA measures for the genu and body of the corpus callosum, left and right tapetum, and left superior fronto-occipital fasciculus in controls. In patients, BMI was significantly positively correlated with white matter FA for the genu of the corpus callosum and left tapetum. Lower BMI was significantly correlated with more severe negative symptoms, as was earlier age of illness onset. Body mass may be differentially associated with fronto-limbic white matter microstructure in first-episode schizophrenia spectrum disorder compared to controls.

1. Introduction

Excessive body mass and schizophrenia are both associated with white matter changes, often affecting the same tracts, including the corpus callosum, fornix, cingulum bundle, and uncinate fasciculus (Kubicki et al., 2005; Shimoji et al., 2013). Studying white matter changes provides a useful neuro-anatomical basis for exploring shared loco-regional changes in brain connectivity reported for both obesity and schizophrenia (Cheung et al., 2008; Lee et al., 2013).

In recent years, diffusion tensor imaging (DTI) in particular has emerged as a useful method for assessing white matter connectivity in vivo (Kanaan et al., 2005) based on measures of water diffusion in the brain, including fractional anisotropy (FA). Increased body mass index as a hallmark of the metabolic syndrome is most often associated with decreased FA in general population studies (Shimoji et al., 2013; Xu et al., 2013). In addition, several studies have shown an association between increased body mass index and decreased white matter FA in bipolar disorder (Kuswanto et al., 2014; Mazza et al., 2017; Reckziegel et al., 2018), as well as in schizophrenia patients (Spangaro et al., 2018) and their at-risk family members (Koivukangas et al., 2016). However, findings to date are inconsistent. Other studies have reported an association between metabolic syndrome risk factors (Tang et al., 2011; Verstynen et al., 2013) including obesity (Ou et al., 2015) and increased FA, while others still have reported increased versus decreased FA across different white matter tracts in both overweight (Carbine et al., 2020) and underweight (Travis et al., 2015) individuals.

Taken together, the weight of the literature suggests a bi-directional relationship between white matter connectivity and metabolic syndrome. Importantly, the direction of causality is often not clear. On the one hand, obesity may lead to changes in brain structure, integrity and connectivity; on the other, altered brain structural and functional connectivity may predispose towards weight gain, not only in the general population (Smucny et al., 2012; Metzler-Baddeley et al., 2013;

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Park et al., 2016), but also schizophrenia patients (Savransky et al., 2017; Homan et al., 2019). In response to these knowledge gaps, the aim of the present study was to investigate the associations of body mass index with white matter FA in minimally treated first-episode schizophrenia spectrum disorder patients compared to healthy controls. We were interested in the fronto-limbic tracts known to connect different brain regions involved in the physiological, cognitive, emotional and reward-based control of eating patterns and behaviours as part of a "core eating network" (Chen et al., 2016) in humans.

Firstly, we hypothesized that body mass index would be differentially associated with fronto-limbic white matter FA in patients versus controls. We anticipated an inverse correlation between body mass index and FA in controls, consistent with that most often reported in general population studies (Stanek et al., 2010; Xu et al., 2013). In addition, we hypothesised that our patients would have a lower body mass index than controls, as previously reported for first-episode schizophrenia spectrum disorders (Sugawara et al., 2018; Shah et al., 2019) and that this would be associated with lower fronto-limbic white matter FA, given the previously reported widespread reductions in fronto-corticoid-limbic white matter FA in schizophrenia versus healthy controls (Price et al., 2008; Schmidt et al., 2015; Asmal et al., 2017, 2019). Lastly, we hypothesized that lower body mass index would be associated with more pronounced psychopathology (Subramanian et al., 2014; An et al., 2018), and that this would be most apparent for negative symptoms (Li et al., 2017; An et al., 2018; Mezquida et al., 2018; Wei et al., 2020).

2. Materials and methods

2.1. Ethics approval

Ethics approval for the present study was obtained from the Health and Research Ethics Committee (HREC) at Stellenbosch University (SU) (N06/08/148). Our study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines (International Conference on Harmonization, 1996). We obtained written, informed consent from participants and where appropriate, from a legal guardian.

2.2. Selection of study participants

The present study included minimally treated first-episode schizophrenia spectrum disorder patients (n =69) and healthy controls (n =93). The patients were recruited from first admissions to hospitals and community clinics in the metro and rural areas of North Eastern Cape Town, the Winelands and the West Coast over a four-year period (2007–2011). Inclusion criteria were men and women, in- or out- patients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria included 1) lifetime exposure to four or more weeks of antipsychotic medication, 2) serious or unstable medical condition, 3) substance-induced psychosis, and 4) intellectual disability. Healthy controls were recruited through word of mouth, community newspaper advertisements, and fliers. Patients and controls were matched for age, sex and ethnicity.

2.3. Clinical assessments

All study participants completed a general medical questionnaire and received a thorough physical examination performed by a study clinician, during which body weight was measured. Participants removed all surplus clothing including their socks and shoes and were weighed on an electronic scale that was regularly calibrated throughout the study. Height was measured with a pre-fixed wall-mounted measuring tape. Body mass index was calculated as the patient's body weight in kilograms (kg) divided by their height in meters squared (m^2). Patients and controls were assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). In addition to PANSS total scores, we considered the positive, negative and disorganized factor-analysis derived symptom domains (Emsley et al., 2003). Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993). Illness severity was estimated with the Clinical Global Impression (CGI) scale (Guy, 1976). Age of onset of psychosis was estimated based on clinical history provided by the family, relatives or caregiver(s) of continuous onset of positive symptoms including delusions, hallucinations, disorganized thinking or bizarre behaviour in patients. In addition, we assessed prior and current substance use based on self-report history. Urine toxicology for cannabis, methamphetamine and methaqualone as the most commonly used substances in our study cohort was also performed. Study participants were classified as "cannabis use positive" or "cannabis use negative".

2.4. Neuroimaging assessment

High-resolution diffusion-weighted images (DWI) were acquired at on an Allegra MRI scanner (Erlangen, Germany) with the following parameters: field of view= 220 mm, spatial resolution= 1.8 mm X 1.8 mm X 1.8 mm^3, repetition time= 8800 ms, echo time= 88 ms, 65 slices, no distance factor with two-fold GRAPPA acceleration. The gradients were applied in 30 directions with b = 1000s/ms^2 and a single unweighted volume (b = 0/mm^2) were also acquired. This sequence was repeated three times. The DWI were pre-processed using the Functional MRI of the Brain (FMRIB) Software Library (FSL) version 4.1.8. Raw DTI data were corrected for eddy current distortions and head motion, and the images were imported into MatLAB. The three acquisitions were co-registered by using the first b = 0 mm/s^2 as the reference image. Outliers were determined based on the Z-value of the tensor images estimated at the 25th and 75th percentiles. Data points falling outside of more than three standard deviations were discarded. The acquisitions were averaged and exported to FSL for further processing.

In an overlapping cohort, we have previously investigated the associations of white matter FA with illness insight (Asmal et al., 2017) and childhood trauma (Asmal et al., 2019) in first-episode schizophrenia. In accordance with other DTI studies (Price et al., 2008; Lee et al., 2013), we found widespread white matter FA reductions. In the present study, we selected a-priori fronto-limbic white matter tracts known to connect different areas of the brain involved in the physiological (e.g. hypothalamus), cognitive-emotional (e.g. orbito-frontal and dorso-lateral prefrontal cortex, hippocampus, amygdala) and hedonic (e.g. ventral tegmental area, nucleus accumbens) control of metabolism, appetite, satiety and reward (Chen et al., 2016). These tracts were: the corpus callosum (body, genu and splenium), fornix, tapetum, superior fronto-occipital fasciculus, fornix crus/stria terminalis, cingulum bundle, cingulum of the hippocampus, and the uncinate fasciculus. Importantly, these tracts are known to be affected in schizophrenia (Price et al., 2008; Kuswanto et al., 2012; Lee et al., 2013).

2.5. Statistical analysis

Statistical analyses were performed using the R software package (3.2.4) and IBM SPSS software program (version 25). Categorical variables were described using cross-tabulation and frequency tables, and compared between patients and controls using a Chi-squared test. Normally distributed numerical data were described as the means along with standard deviation, and compared between study groups (e.g. patient versus control, male versus female) using a student's t-test. If the best-fitting log-transformation of non-normal continuous data remained

so, they were described as the median along with inter-quartile range, and compared between groups using the Wilcoxon rank sum test. For our main analysis, fronto-limbic white matter FA measures across the abovementioned tracts of interest were entered as dependant variables into a multivariate analysis of covariance (MANCOVA) modelling for the interaction between study group (patient versus control) and body mass index, adjusting for age, sex and cannabis use as covariates. Pearson correlation coefficients were then used to investigate the specificity and directionality of findings evident from our main analyses (i.e. the associations of body mass index with fronto-limbic white matter in patients versus controls), as well as to explore the associations of body mass index with age of psychosis onset, global illness severity (CGI), psychopathology (PANSS total scores, positive, negative, disorganized domains) and depressive symptoms (CDSS) in patients. A p-value of <0.05 was used to indicate statistical significance.

3. Results

3.1. Characteristics of study group

The present study included 69 patients and 93 controls, matched for age, sex and ethnicity (Table 1). Body mass index was significantly lower in patients (21.37 kg/m^2) versus controls (23.76 kg/m^2) ($t = 2.99, p<0.01$). The distribution of body mass index categories also differed significantly between these two groups ($X^2 = 10.70$, $p = 0.013$), with a preponderance of overweight and particularly obese participants in controls compared to the patient group (Table 1). In controls, body mass index was significantly lower in males compared to females ($t = -4.19$, $p<0.01$), as well as cannabis users compared to non-users ($t = -3.75$, $p<0.01$). These differences were however not significant in the patient group ($p<0.05$).

3.2. Associations of body mass index with fronto-limbic white matter fa in patients versus controls

MANCOVA identified a significant interaction between body mass index and group (patient versus control) across the fronto-limbic white matter tracts of interest, independent of age, sex and cannabis use ($F(1155) = 4.91$, $p = 0.03$). In a sub-analysis, we found significant inverse correlations between body mass index and FA measures for the genu ($r = -0.21$, $p = 0.04$) and body ($r = -0.27$, $p<0.01$) of the corpus callosum, the left tapetum ($r = -0.25$, $p = 0.01$) and right tapetum ($r = -0.27$, $p<0.01$), as well as the left superior fronto-occipital fasciculus ($r = -0.21$, $p = 0.04$) in controls. In contrast, body mass index was significantly positively correlated with FA measures for the genu of the corpus callosum ($r = 0.27$, $p = 0.03$) and left tapetum ($r = 0.26$, $p = 0.03$) in patients. In summary, there was a differential association of body mass index with FA for the genu of the corpus callosum and left tapetum in the patient group (decreased body mass index, decreased FA) versus controls (increased body mass index, decreased FA) (Fig. 1).

3.3. Associations of body mass index with illness severity and symptom profile in patients

Lower body mass index was significantly associated with an earlier age of psychosis onset ($r = 0.26$, $p = 0.03$) and more pronounced negative symptoms ($r = -0.28$, $p = 0.02$). However, there were no significant associations between body mass index and overall illness severity (CGI), global psychopathology (PANSS total scores), the positive and disorganized factor-derived domains, or depressive symptoms (CDSS scores) ($p>0.05$).

4. Discussion

In this study, we report differential associations of body mass index with fronto-limbic white matter microstructure in minimally treated, first-episode schizophrenia spectrum disorder patients (decreased body mass index associated with decreased FA) compared to healthy, matched controls (increased body mass index associated with decreased FA). Importantly, we found widespread involvement of white matter tracts which form part of the cortico-limbic circuitry connecting key brain regions involved in the physiological (e.g. hypothalamus, certain brainstem nuclei), cognitive-emotional (e.g. dorso-lateral prefrontal cortex, orbito-frontal cortex, amygdala, hippocampus) and reward-based (e.g. ventral striatum, nucleus accumbens) regulation of appetite, satiety and diet as part of a “core eating network” (Chen et al., 2016). This study is to the best of our knowledge the first to report relationships between body mass index, white matter FA and symptom profiles in first-episode schizophrenia spectrum disorders.

Our finding that higher body mass index was significantly correlated with lower FA measures across multiple fronto-limbic tracts in our control group, more than a fifth (22%) of whom were obese, is in keeping with most general population studies (Stanek et al., 2010; Xu et al., 2013). Evidence suggests that obesity-driven mechanisms, including oxidative stress, inflammation, immune dysregulation, and

Table 1
Socio-demographic and clinical characteristics of study group compared between patients and controls.

	Patients ($n = 69$)	Controls ($n = 93$)	Patient versus control (unadjusted p-value)
Age (years) (mean/SD)	24.43 (6.56)	25.80 (7.48)	0.22
Sex (male,%)	49 (71%)	59 (63%)	0.40
Highest level of education (years of schooling completed) (mean/SD)	9.93 (1.99)	10.44 (1.51)	0.10
BMI (kg/m^2)	21.37 (3.88)	23.76 (6.29)	<0.01
BMI classification			
Underweight (<18.5 kg/m^2)	12 (17%)	16 (17%)	0.01
Normal weight (18.5–25.0 kg/m^2)	47 (68%)	42 (45%)	
Overweight (25–30.0 kg/m^2)	8 (12%)	15 (16%)	
Obese (>30 kg/m^2)	2 (3%)	20 (22%)	
Cannabis use (yes,%)	20 (29%)	28 (30%)	1.00
Treatment-naive (yes,%)	44 (64%)		–
Duration of treatment in non-naive patients, days (mean/SD)	11.60 (7.11)		–
Age of psychosis onset (mean/SD)	23.90 (7.17)		
PANSS Total score (mean/SD)	92.57 (15.64)		–
PANSS Positive symptom factor-analysis derived domain (mean/SD)	17.23 (3.44)		–
PANSS Negative symptom factor-analysis derived domain (mean/SD)	19.09 (5.12)		–
PANSS Disorganized symptom factor-analysis derived domain (mean/SD)	11.51 (3.12)		–
Clinical Global Impression scale (mean/SD)	3.72 (0.62)		–
Calgary Depression Scale for Schizophrenia (mean/SD)	3.57 (4.28)		–

BMI = body mass index; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

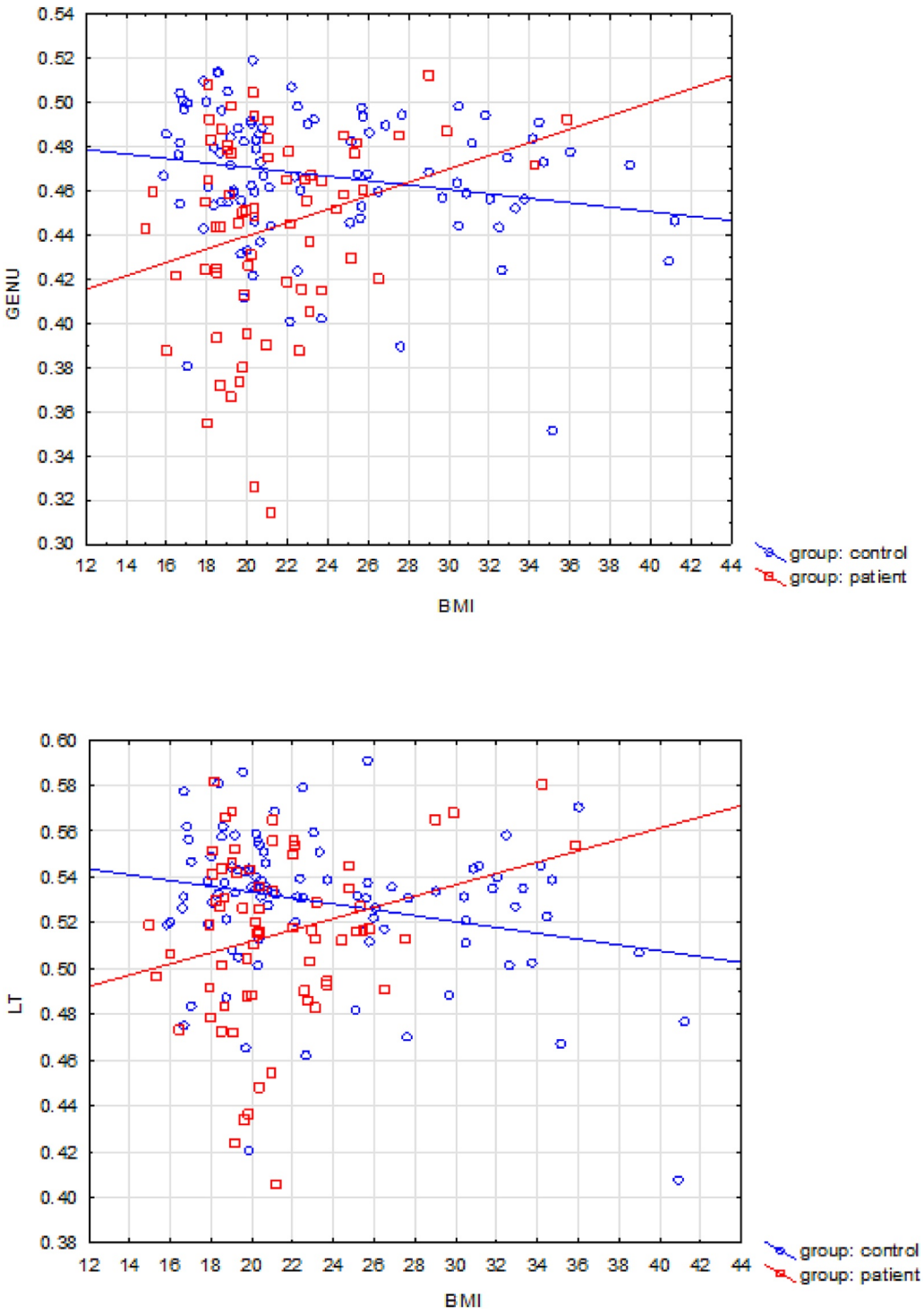

Fig. 1. Scatterplot diagrams showing the differential associations of body mass index (BMI) with fractional anisotropy (FA) measures for the genu of the corpus callosum (above) and left tapetum (below) in patients versus healthy controls. In patients, BMI was positively correlated with white matter FA for these tracts; in contrast, an inverse correlation between BMI and white matter FA was evident for healthy controls.

hypothalamic-pituitary-adrenal (HPA) axis dysfunction, may contribute to changes in white matter microstructure, integrity and connectivity (Kullman et al., 2016; Samara et al., 2019). On the other hand, an explanation for the association of low body mass index with low fronto-limbic white matter FA in our patient sample is less clear, although general population studies have reported decreased white matter integrity across several central tracts (including the anterior, frontal and orbital regions of the corpus callosum) in normal and under-weight compared to overweight individuals (Carbine et al., 2020). In addition, similar findings to ours have been reported in patients with restrictive eating disorders, in whom widespread reductions in fronto-limbic white matter FA associated with lower body mass index have been reported when compared to healthy controls (Hu et al., 2017; Nickel et al., 2019). In particular, involvement of inter-hemispheric (e.g. corpus callosum) white matter tracts is consistent with the fronto-cortico-limbic circuitry described here under the “core eating network”. Our finding for the left tapetum, which is mainly comprised of decussating fibers in the splenium (Sarikcioglu et al., 2007) of the corpus callosum,

is of interest, since structural abnormalities of the tapetum have also been linked to more severe positive symptoms and a longer duration of untreated psychosis (Lee et al., 2018).

A possible neurobiological explanation for our findings in patients could lie in the fact that oligodendrocytes are highly energy-dependant, with effective myelination being dependant on a favourable metabolic milieu (Bartzokis et al., 2007). Important micro-nutrient deficiencies associated with impaired myelination capacity (Bartzokis, 2011), including decreased iron, folate and vitamin B12 levels, have been reported in schizophrenia (Williamson et al., 2015; Firth et al., 2018). In addition to overeating, restrictive eating patterns and underweight have been described in schizophrenia patients (Kouidrat et al., 2014). Emerging literature further suggests that treatment-naïve patients with first-episode schizophrenia respond differently to food cues, and this in turn may affect changes in appetite and metabolic status over the course of antipsychotic treatment (Stip et al., 2012; Borgan et al., 2019). Low body mass index may therefore be a proxy measure for micro-nutrient deficiencies and secondary metabolic abnormalities associated with poorer myelination capacity (Takahashi et al., 2011; Maas et al., 2017).

In keeping with the effects of weight gain as a predictor of psychopathology improvement in first-episode psychosis (Luckhoff et al., 2019a), multiple studies have shown that lower body mass index is associated with more severe psychopathology in schizophrenia (Subramanian et al., 2014; An et al., 2018). In particular, negative symptoms have been associated with lower body mass index in chronic patients (Li et al., 2017; Mezquida et al., 2018; Wei et al., 2020) and those at clinical high-risk for psychosis (Caravaggio et al., 2017), which is similar to our finding in this first-episode sample. This is also consistent with our previous findings of an unfavourable association between low baseline body mass index and poorer end-point working memory performance after 12 months of treatment first-episode psychosis, at least for cannabis users (Luckhoff et al., 2019b). Furthermore, low body mass index has been linked with poorer treatment outcomes in schizophrenia across multiple domains, including treatment failure (Chiliza et al., 2015), a longer time to respond to treatment (Schwarz et al., 2012) and shorter time to relapse (Stauffer et al., 2011).

There are several possible explanations for the correlation between lower body mass index and more pronounced negative symptoms evident from our study, which remained significant when adjusting for sex and cannabis use. Firstly, certain negative symptoms, particularly anhedonia, may contribute to poor self-care and diet, reflected by a lower body mass index in patients (Mezquida et al., 2018). Also, other negative symptoms, including social withdrawal and a sedentary lifestyle, may affect diet, exercise and eating patterns, thereby contributing to weight gain (Dipasquale et al., 2013; Sicras-Mainar et al., 2014; Storch-Jakobsen et al., 2018; Ulloa et al., 2018). However, dietary and lifestyle factors are unlikely to fully explain the consistently reported link between low body mass index and negative symptoms. Finally, body mass index may serve as a proxy marker for other determinants of illness severity (Chiliza et al., 2015). For example, an earlier age of onset has emerged as an important predictor of greater illness severity, more pronounced negative symptoms, psycho-social impairment, and poorer treatment outcomes in schizophrenia (Kao and Liu, 2010; Immonen et al., 2017). Indeed, we found that age of onset was significantly correlated with negative symptoms ($r = -0.37$, $p = 0.001$). Furthermore, an association between lower body mass index and an earlier age of onset has been reported (Wei et al., 2020), although another study did not find this (Nadalin et al., 2018).

The identification of body mass index as a metabolic correlate of negative symptom severity in our study could have implications for patient care. Our findings for body mass index, age of onset and negative symptoms as inter-related determinants of illness severity and treatment outcome hint at an extended role for metabolic assessment beyond cardiovascular risk screening to include clinical prognostication in first-episode psychosis. The definition and conceptualization of negative symptoms, as well as our understanding of their temporal course, clinical burden, and effects on treatment outcome, have undergone considerable developments in recent years (Correll and Schooler, 2020). Since the accurate assessment of negative symptoms is critical to their appropriate management, new instruments have been developed to assess them, such as the Brief Negative Symptom Scale (Kirkpatrick et al., 2011) and Clinical Assessment Interview for Negative Symptoms (Kring et al., 2013). The use of the PANSS to assess negative symptoms has been subject to criticism (Lindenmayer, 2017; Correll and Schooler, 2020). Numerous factor analytical studies have identified a negative symptom domain that differs on several items from the original negative subscale (Emsley et al., 2003). For that reason, we opted to calculate a factor analysis-derived negative symptom domain. This echoes the approach used in our prior research examining the associations of metabolic syndrome risk factors for psychopathology improvement in first-episode schizophrenia spectrum disorders (Luckhoff et al., 2019a). The value of factor-analysis in exploring the relationship between body mass index and negative symptoms was further described in a study of chronic schizophrenia patients conducted by Mezquida et al. (2018).

Our study had several important strengths. Firstly, we included a well-characterized patient sample, and could minimise the confounding effects of prior treatment exposure, since cases were largely antipsychotic-naive. Secondly, our study had a relatively large sample size, and included a matched, healthy control group. Thirdly, we used a validated methodological approach for tract-based comparison of white matter FA using a previously described neuroimaging protocol (Asmal et al., 2017, 2019). However, several limitations are also acknowledged. Firstly, we focused on body mass index rather than other anthropometric measures, and did not include other metabolic syndrome features in this analysis. In addition, this was a cross-sectional study, unable to assess longitudinal changes in our sample. Secondly, our sample was collected from a largely socio-economically disadvantaged population, and as such, it may not always be possible to generalize our results to other patient populations. Thirdly, although our sample is relatively large for a single-site DTI study, we lacked statistical power to detect more subtle associations. Fourthly, as described above, use of a specific scale for negative symptoms may have better assessed this symptom domain. Finally, as we did not correct for multiple comparisons, our findings should be considered to be hypothesis-generating only.

5. Conclusions

We found that body mass index was differentially associated with fronto-limbic white matter FA in first-episode schizophrenia spectrum disorder patients compared to healthy controls. While we replicated an association between overweight and reduced FA in healthy controls, a reverse association was found in patients, that may be linked to age of onset of illness and severity of negative symptoms. Future studies should examine the temporal effects of antipsychotic exposure on white matter microstructure, changes in body mass, and treatment outcome in first-episode schizophrenia spectrum disorders. More research is needed on how different weight gain trajectories over the course of treatment are related to sub-cortical brain regions involved in the regulation of appetite and satiety in humans.

Contributors

All authors contributed equally to the manuscript.

Declaration of Competing Interest

Robin Emsley has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka. Hilmar

Luckhoff, Lebogang Phahladira, Freda Scheffler, Retha Smit, Chanelle Buckle, Stefan du Plessis, Laila Asmal, and Sanja Kilian declare that they have no conflicts of interest.

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CHAPTER FIVE

Hippocampal subfield volumes and change in body mass index over 12 months of flupenthixol decanoate treatment in first-episode schizophrenia spectrum disorders

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Hippocampal subfield volumes and change in body mass over 12 months of treatment in first-episode schizophrenia spectrum disorders

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ABSTRACT

In this study, we explored the relationship between baseline hippocampal subfield volumes and change in body mass over 12 months of treatment in 90 first-episode schizophrenia spectrum disorder patients (66 males, 24 females; mean age = 24.7 ± 6.8 years). Body mass index was assessed in patients at baseline, and at months 3, 6, 9 and 12. Hippocampal subfields of interest were assessed at baseline using a segmentation algorithm included in the FreeSurfer 6.0 software program. Linear regression revealed a significant interactive effect between sex and anterior hippocampus size as predictors of change in body mass over 12 months, adjusting for age, substance use, and treatment duration. In an exploratory post-hoc sub-analysis, partial correlations showed a significant association between weight gain and smaller CA1, CA3 and subiculum volumes in females, but not males, adjusting for age and substance use, with similar trends evident for the CA4 and presubiculum subfields. In conclusion, our findings suggest that smaller anterior hippocampal subfields at baseline are associated with the development of weight gain over the course of treatment in first-episode schizophrenia spectrum disorders in a sex-specific fashion. This may be related to the greater increase in body mass evident for female patients in our study.

1. Introduction

Hippocampal structural and functional abnormalities are implicated in the pathophysiology of schizophrenia (Heckers and Konradi, 2002; Lieberman et al., 2018). In addition to widespread bilateral volume reductions as a consistent finding in both first-episode and chronic schizophrenia (Velakoulis et al., 2006; Adriano et al., 2012) localized changes across different hippocampal regions have also been reported early in the disease state (Li et al., 2018). In particular, more anterior subfields including the cornus ammonis (CA) and subiculum regions are preferentially affected in first-episode schizophrenia, with extension to include more posterior regions as the illness progresses (Narr et al., 2004; Kawano et al., 2015; Ho et al., 2017; Ota et al., 2017; Baglivo et al., 2018; Haukvik et al., 2018; McHugo et al., 2018; Nakahara et al., 2018). Moreover, smaller hippocampal subfield volumes may predict illness onset in those at high-risk for psychosis, and have been associated with more severe psychopathology and poorer cognitive performance in some (Kuhn et al., 2012; Zierhut et al., 2013; Makowski et al., 2017; Ota et al., 2017) but not all (Kawano et al., 2015; Baglivo et al., 2018) studies. Hippocampal subfield volume alterations could therefore represent an important biological marker in first-episode schizophrenia (Nakahara et al., 2018).

The hippocampus is functionally related to other brain regions which form part of a "core eating network" in humans (Chen et al., 2018). In this context, the hippocampus plays an important part in the cognitive control of eating, in keeping with its role in memory consolidation and reward-based decision-making (Davidson et al., 2007; Berthoud et al., 2017; Kanoski and Grill, 2017; Higgs and Spetter, 2018). Hippocampal dysfunction is therefore associated with greater responsiveness to food intake and satiety cues, leading to increased appetite and resultant weight gain (Hargrave et al., 2016; Mestre et al., 2017). Importantly, since hippocampal neurons are highly susceptible to vascular injury, increase in body mass in turn may contribute to structural damage to the hippocampus, as evident in the general population (Taki et al., 2008; Cherbuin et al., 2015). Increased body mass has also been correlated with smaller brain volumes in both schizophrenia (Emsley et al., 2015) and bipolar disorder (Bond et al., 2011, 2014). However, findings for the hippocampus remain largely unclear (Viana-Sulzbach et al., 2016; Bond et al., 2017). In particular, little is known about how structural and functional hippocampal

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abnormalities could influence change in body mass over time in first-episode schizophrenia. This is important, since treatment-naive patients are predisposed towards the development of weight gain and other metabolic syndrome changes (Strassnig et al., 2007). Indeed, altered structural and functional connectivity of brain regions implicated in reward processing, memory consolidation, appetite regulation, arousal and salience has been shown to differentiate between obese and normal-weight individuals in the general population (Gupta et al., 2015; Park et al., 2018). In this context, structural variation across different sub-cortical areas including the striatum (Homan et al., 2019) and hippocampus (Letourneau et al., 2011) implicated in appetite regulation and food intake could play a role in antipsychotic-induced weight gain in schizophrenia patients.

These observations provided the scientific rationale for the present study, in which we sought to investigate the influence of anterior hippocampal subfield volumes as predictors of change in body mass trajectories of 12 months of treatment, in relation to age, sex, baseline body mass, and substance use. We focused our analysis on the hippocampus as an important food intake control center (Liu and Kanoski, 2018) involved in regulation of appetite, energy homeostasis, and metabolism (Cenquizca and Swanson, 2006). Our focus on weight gain was motivated by a significant increase in BMI over 12 months evident in our larger study sample (Chiliza et al., 2015) which correlated with both psychopathology improvement (Luckhoff et al., 2019a) and better end-point cognitive performance including working memory (Luckhoff et al., 2019b). Firstly, we hypothesized that smaller subfield volumes, particularly for the anterior hippocampus preferentially affected in early schizophrenia (Nakahara et al., 2018) and obesity (Mole et al., 2016), would be associated with weight gain. Secondly, given known differences in brain volume and risk for metabolic syndrome evident between male and female schizophrenia patients, we hypothesized that this effect would be sex-specific (Kraal et al., 2017; Egloff et al., 2018).

2. Methods

2.1. Ethics approval and study design

Ethics approval for the present longitudinal study was obtained from the Health and Research Ethics Committee (HREC) at Stellenbosch University (SU) (N06/08/148). We obtained written, informed consent from participants and where appropriate, from a legal guardian. The present study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Selection of study participants

The present study included first-episode, largely treatment-naïve schizophrenia spectrum disorder patients recruited from first admissions to hospitals and community clinics in the metro and rural areas of North Eastern Cape Town, the Winelands and the West Coast over a four-year period (2007–2011). Inclusion criteria were men and women, in- or out- patients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV-TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria included 1) lifetime exposure to four or more weeks of antipsychotic medication, 2) serious or unstable medical condition, 3) substance-induced psychosis, and 4) intellectual disability. Healthy controls were recruited from the same catchment areas through either personal contact or advertisements.

2.3. Antipsychotic treatment

Patients were treated with flupenthixol decanoate. Long-acting injectable antipsychotics improve adherence and have demonstrated efficacy and tolerability when used in the early phase of illness (Emsley et al., 2013). Treatment was initiated based on a fixed protocol, with a lead-in period of seven days, during which patients were treated with oral flupenthixol 1–3 mg/daily followed by flexible doses of flupenthixol decanoate (starting dose = 10 mg intramuscular two-weekly). The lowest possible dosage was maintained, and medication was only increased when treatment response was insufficient. Lorazepam, biperiden, orphenadrine, propranolol and antidepressants were permitted as concomitant medications. However, to minimize the potential effects of additional treatment on metabolic status, benzodiazepines, anticholinergic medications and propranolol were not allowed within 12 h of the time of assessment. Additional prohibited medications included other antipsychotics, mood stabilizers and psychostimulants.

2.4. Patient assessments

Body weight was measured at baseline and again at months 3, 6, 9 and 12. Patients were asked to remove all surplus clothing and weighed on an electronic scale that was calibrated regularly throughout the study. Height was measured with a pre-fixed wall-mounted measuring tape to the nearest centimetre (cm). Body mass index (BMI) was calculated as the body weight of the patient in kilograms (kg) divided by their height in meters squared (m2). Urine toxicology for cannabis, methaqualone and methamphetamine (the most frequently used substances in the patient community) was performed at baseline, and again at months 3, 6 and 12. Patients were classified as substance use positive if they tested positive for any of these substances over the course of the study.

2.5. Structural magnetic resonance imaging

High-resolution T1-weighted data were acquired on an3T Allegra MRI scanner (Erlangen, Germany) at the Cape Universities Brain Imaging Center (CUBIC), Tygerberg, Cape Town. All scans were screened by an experienced radiologist for intracranial pathology and inspected for motion artefacts. In total, 95 patients and 98 controls were scanned at baseline using an MPRAGE sequence (2080 ms repetition time; 4.88 ms echo time, Field of view: 230 mm, 176 slices, 0.9 mm X 0.9 mm X 1 mm voxel size). Five patients and six controls were excluded based on inferior scan quality, thus the analysis sample comprised 90 patients and 92 controls.

2.5.1. Image pre-processing

Scans were processed and analysed using FreeSurfer stable release version 6.0. (http://surfer.nmr.mgh.harvard.edu) (Fischl, 2012). Briefly, slices were re-sampled to a three-dimensional image with 1 mm isotropic voxels. Non-uniform intensity normalization was then performed, after which images were registered to the Montreal Neurological Institute (MNI) space. A second normalization step was then performed with a different algorithm in which control points were automatically identified and normalized to a standard intensity value, followed by an automated skull strip procedure. Gross brain anatomy was delineated into cortical and subcortical labels. Reconstructions were performed with custom batching scripts on the center for High Performance Computing (CHPC) (Rosebank, Cape Town) Sun Intel Lengau cluster (http://www.chpc.ac.za/).

2.5.2. Hippocampal subfield segmentation

Subfields were segmented using an algorithm included in FreeSurfer 6.0 which is based on a computational atlas built from ex-vivo MRI data of postmortem medial temporal tissue acquired on a 7 Tesla scanner as well as an in-vivo atlas which provided information regarding adjacent extra hippocampal structures (Iglesias et al., 2015). All subfields were corrected for estimated total intracranial volume. In order to further limit the number of analyses performed, left and right hippocampal

volumes for the subfields were summed. Subfield volumes were also log-transformed prior to analyses. We grouped the subfields into anterior and posterior hippocampal subfields, as previously described (Zeidman and Maguire, 2016; Zeidman et al., 2016). Anterior hippocampal subfields of interest included the CA1, CA3 and CA4 subregions, as well as the subiculum, presubiculum, and parasubiculum. In comparison, posterior subfields of interest included the granule cell layer of the dentate gyrus, (GC), molecular layer of the dentate gyrus (ML), hippocampus–amygdala transition area (HATA), hippocampal tail, and fimbria.

2.6. Statistical analysis

Statistical analysis was performed using R Studio software. Categorical data (e.g. sex, substance use) were described as percentages or frequencies, and compared between patient groups using a Chi-squared or Fisher's exact test, as appropriate. For numerical data, normality of distribution was established using the Shapiro-Wilk test. Normally distributed data were described as the means along with standard deviation (SD). Non-normal data was log-transformed prior to analysis. If the best-fitting log-transformed data was still not normally distributed, data were described as the median along with interquartile range. Analysis of variance was used to compare continuous numerical data between patients and controls. End-point scores for BMI were calculated as the last observation carried forward (LOCF). BMI change scores were calculated as the difference between the end-point and baseline scores. Linear mixed models for repeated measures (MMRM) were used to assess visit-wise changes in body mass over time, incorporating fixed terms for age, sex, and substance use. Linear regression models and partial correlations were used to explore the influence of hippocampal volumes on change in body mass over time in relation to age, sex, substance use, and antipsychotic treatment duration. The Benjamini-Hochberg method was used to correct for multiple comparisons in our post-hoc analyses. A p-value of 0.05 was used to indicate statistical significance, while a p-value below 0.10 was used to indicate trend associations.

3. Results

3.1. Baseline characteristics of study sample

The present study included 90 minimally treated or antipsychotic-naive patients with first-episode psychosis (66 male, 24 female; mean age = 24.7 ± 6.8 years) and 92 healthy controls (57 males, 35 females, mean age = 25.8 ± 7.5 years). There was no significant difference between patients and controls for age or sex (Table 1).Hippocampal subfield volumes of interest (i.e. CA1, CA3, CA4, subiculum, presubiculum, parasubiculum, granule cell layer of the dentate gyrus, molecular layer of the dentate gyrus, hippocampal-amygdala transition area, tail and fimbria) did not differ significantly between patients and controls (Table 1). However, baseline body mass was significantly lower in patients compared to controls ($p = 0.011$).

3.2. Characteristics of patient group

The majority of patients had a DSM-IV-TR diagnosis of schizophrenia ($n = 62$, 69%), while 27 patients (30%) were diagnosed with schizophreniform disorder, and one patient (1%) had a diagnosis of schizoaffective disorder. Our sample consisted mostly ($n = 72$; 74%) of patients of Mixed Ancestry, and also included 13 Black African (15%) and five Caucasian (11%) patients. A total of 34 patients (38%) were classified as substance use positive based on urine toxicology for cannabis, methamphetamine or methaqualone use. Mean treatment duration was 42 weeks. The mean modal dose of flupenthixol decanoate was 10 mg in 45 patients, 15 mg in 18 patients, 20 mg in nine patients, 5 mg in three patients, and 25 mg in one patient. Male patients were significantly more likely to report a history of substance use ($p = 0.018$), while females tended to be older ($p = 0.063$).In accordance with prior studies conducted in first-episode schizophrenia samples (Egloff et al., 2018), we found that, while male patients had larger total intracranial volumes, all corrected hippocampal subfield volumes except the fimbria were significantly larger in female patients, as shown in Table 2.

3.3. Change in body mass index over 12 months of treatment in patients

MMRM analysis showed a significant sex*time interaction ($p = 0.01$) (Fig. 1), whereby female patients (least significant difference = 4.89 kg/m^2) gained weight to a greater extent over the course of the study than males (least significant difference = 2.29 kg/m^2), adjusting for age and substance use. In total, 72 patients had at least one post-baseline body mass assessment used to determine weight gain over time. From this subgroup, 52 patients (72%) had complete data for all body mass index assessments, including for month 12. In comparison, six patients (8%) had their last assessment at month 9, seven patients (10%) had their last assessment at month 6, while another seven patients (10%) had only one follow-up body mass assessment at month 3.

3.4. Hippocampal volumes as a predictor of weight gain in patients

In the total patient sample, there were no significant correlations between baseline body mass and hippocampal subfield volumes ($p > 0.05$). In addition, we failed to demonstrate a significant correlation between weight gain (i.e. the BMI change score) and either anterior (rho = −0.10, $p = 0.327$) or posterior (rho = −0.07, $p = 0.506$)

Table 1
Comparison of hippocampal subfield volumes between patients and controls.

Patient characteristic	Patients ($n = 90$) mean (SD)	Controls ($n = 92$) mean (SD)	Unadjusted p-value (patient vs. controls)
Age (years)	24.73 (6.81)	25.80 (7.47)	0.318
Sex (male/female)	66 (73%), 24 (27%)	57 (62%), 35 (38%)	0.139
Body mass index (kg/m^2)	21.76 (4.04)	23.75 (3.56)	0.011*
CA1	0.082 (0.010)	0.084 (0.011)	0.185
CA3	0.029 (0.003)	0.029 (0.004)	0.721
CA4	0.034 (0.004)	0.034 (0.004)	0.636
Subiculum	0.056 (0.007)	0.057 (0.007)	0.202
Presubiculum	0.038 (0.005)	0.039 (0.005)	0.053
Parasubiculum	0.007 (0.001)	0.008 (0.001)	0.130
Granule cell layer of the DG	0.039 (0.004)	0.040 (0.005)	0.449
Molecular layer of the DG	0.074 (0.009)	0.076 (0.009)	0.114
Hippocampus–amygdala transition area	0.012 (0.002)	0.012 (0.002)	0.140
Hippocampal tail	0.072 (0.011)	0.075 (0.012)	0.103
Fimbria	0.010 (0.002)	0.010 (0.002)	0.488

Abbreviations: CA = cornus ammonis; DG = dentate gyrus.

Table 2
Comparison of baseline socio-demographic and clinical characteristics as well as hippocampal subfield volumes between male and female patients. .

Patient characteristics	Male patients (n = 66) mean (SD)	Female patients (n = 24) mean (SD)	Unadjusted p-value (male vs. female)
Age (years)	23.92 (6.19)	26.96 (8.03)	0.061
History of substance use (yes/no)	31 (47%), 35 (53%)	4 (17%), 20 (83%)	0.018
Body mass index (kg/m^2)	21.45 (3.36)	22.61 (5.49)	0.229
Total intracranial volume (ICV) (cm^3)	1591.83 (143.17)	1341.23 (159.68)	<0.001
CA1 vol (mm^3)	0.080 (0.009)	0.086 (0.010)	<0.001
CA3 vol (mm^3)	0.028 (0.003)	0.030 (0.004)	<0.001
CA4 vol (mm^3)	0.033 (0.003)	0.037 (0.004)	<0.001
Subiculum volume (mm^3)	0.054 (0.006)	0.061 (0.009)	<0.001
Presubiculum volume (mm^3)	0.036 (0.004)	0.041 (0.005)	<0.001
Parasubiculum (mm^3)	0.007 (0.001)	0.008 (0.001)	0.002
Granule cell layer of the DG (mm^3)	0.038 (0.003)	0.042 (0.005)	0.002
Molecular layer of the DG (mm^3)	0.072 (0.007)	0.079 (0.011)	<0.001
Hippocampus–amygdala transition area (mm^3)	0.011 (0.001)	0.012 (0.002)	0.010
Hippocampal tail (mm^3)	0.069 (0.009)	0.079 (0.012)	<0.001
Fimbria (mm^3)	0.010 (0.002)	0.010 (0.002)	0.725

Abbreviations: CA = cornusammonis; DG = dentate gyrus.

hippocampal volumes in the total patient group. Linear regression models were then used to explore the interactive effect of sex and hippocampal volumes (sex*volume) on change in body mass over 12 months (dependent variable) in relation to age, substance use, and treatment duration as covariates. In this analysis, we did not include baseline body mass, since it was neither a significant predictor of weight gain, nor significantly correlated with baseline hippocampal subfield volumes in the total patient sample. In addition, we did not include antipsychotic dose in our prediction models, since it was not associated with weight gain in patients, consistent with findings evident in our larger study cohort (Chiliza et al., 2015).

In model one (R^2 = 0.28, F(6,64) = 4.22, p = 0.001) there was a significant interaction between sex and anterior hippocampal volumes (beta = −7.78, p = 0.001) as predictors of change in body mass over 12 months, adjusting for age, substance use, and treatment duration. Individual effects for sex, hippocampal volume and treatment duration were also evident (Table 3). In contrast, no such interaction was evident in model two, where posterior hippocampal volumes and sex were not significant predictors of weight gain (Table 3).

Secondly, we used partial correlations to assess the relationships between individual anterior subfields and change in body mass based on these findings, with patients stratified according to sex. There were no significant associations between change in body mass and any of the anterior hippocampal subfields of interest in male patients. In contrast, in female patients, smaller anterior hippocampal subfield volumes at baseline were correlated with weight gain, adjusting for age and

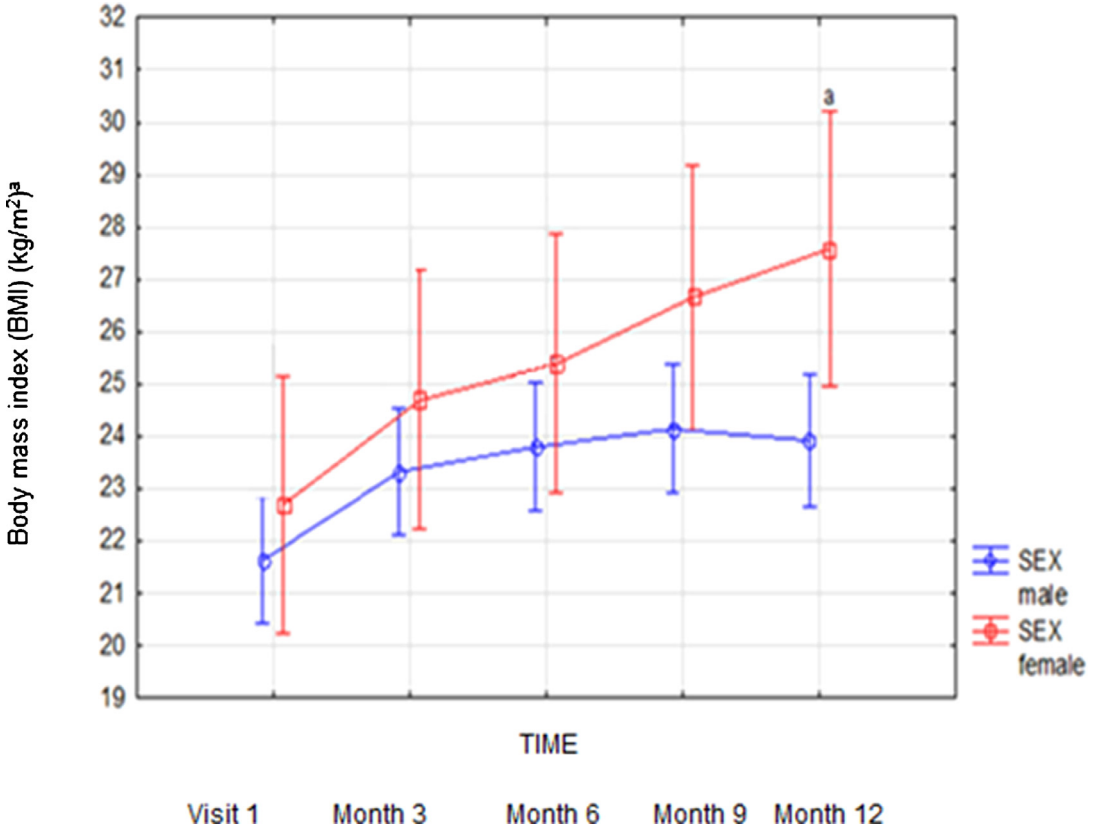

Fig. 1. Comparison of visit-wise change in mean body mass index (BMI) for visit one (baseline) to month 12 (end-point) between male and female patients. [a]: BMI measured in kilograms (kg) per meter squared (m^2) [kg/m^2].

Table 3
Linear regression models showing the interactive effects between sex and hippocampal volume as predictors of change in body mass over 12 months in relation to age, substance use and treatment duration as covariates.

MODEL 1: R^2 = 0.28, F(6,64) = 4.22, p = 0.001			
	Predictors		
	Beta-coefficient	T-value	*p*-value
SEX (male/female)	−66.35	−3.23	0.002
AHV	3.03	2.03	0.046
AGE (years)	−0.05	−1.10	0.278
TREATMENT DURATION (weeks)	0.06	2.26	0.027
SUBSTANCE USE (yes/no)	−1.27	−1.98	0.052
SEX*AHV (interaction)	−7.70	−3.32	0.001
MODEL 2: R^2 = 0.19, F(6,64) = 2.42, p = 0.036			
	Predictors		
	Beta-coefficient	T-value	*p*-value
SEX (male/female)	−20.37	−1.27	0.209
PHV	2.18	1.16	0.250
AGE (years)	−0.06	−1.30	0.198
TREATMENT DURATION (weeks)	0.06	1.98	0.053
SUBSTANCE USE (yes/no)	−1.11	−1.58	0.119
SEX*PHV (interaction)	−2.84	−1.39	0.170

Abbreviations: AHV = anterior hippocampal volume; PHV = posterior hippocampal volume.

substance use (p = 0.026) (Fig. 2). In addition, weight gain was correlated with smaller CA1 (p = 0.033), CA3 (p = 0.027) and subiculum (p = 0.006) volumes in female patients, adjusting for the same confounders. Similar trends were evident for the CA4 (p = 0.056) and presubiculum subfields (p = 0.056) in female patients. The association between smaller subiculum volumes and increase in body mass remained when adjusting for multiple comparisons (adjusted p-value = 0.042).

4. Discussion

In the present study, there was a significant interactive effect between sex and anterior hippocampal volumes on change in body mass over 12 months in first-episode schizophrenia spectrum disorder patients, adjusting for age, substance use, and treatment duration. In an exploratory post-hoc analysis, smaller hippocampal subfield volumes were associated with weight gain in female, but not male patients, independent of age and substance use. Importantly, the association between smaller subiculum volumes and increase in body mass in female patients remained significant following correction for multiple comparisons. Our findings are consistent with the known association between increased body mass and hippocampal structural abnormalities in the general population (Taki et al., 2008; Cherbuin et al., 2015) as well as in chronic schizophrenia patients treated with olanzapine (Letourneau et al., 2011). However, our study extends previous research, and is to the best of our knowledge the first to demonstrate an association between anterior hippocampal size and weight gain in first-episode schizophrenia patients.

The hippocampus is a particularly stress-sensitive brain region, and multiple studies have shown that increased body mass contributes to hippocampal volume loss via several mechanisms, including altered cortisol metabolism and hypothalamic-pituitary-adrenal axis dysregulation. These factors are in turn associated with excitotoxicity, dendritic damage, and neuronal cell death, ultimately leading to impairment in structural integrity of the hippocampus (Mondelli and Howes, 2014; McEwen et al., 2016). However, emerging evidence also shows the importance of the hippocampus in the regulation of food intake and satiety (Hargrave et al., 2016) due in part to its involvement in memory, inhibition and decision making (Davidson et al., 2019). Indeed, the hippocampus is intimately connected to other components of the "core eating network" in humans, and is active at the interface between the physiological, hedonic and cognitive control of eating

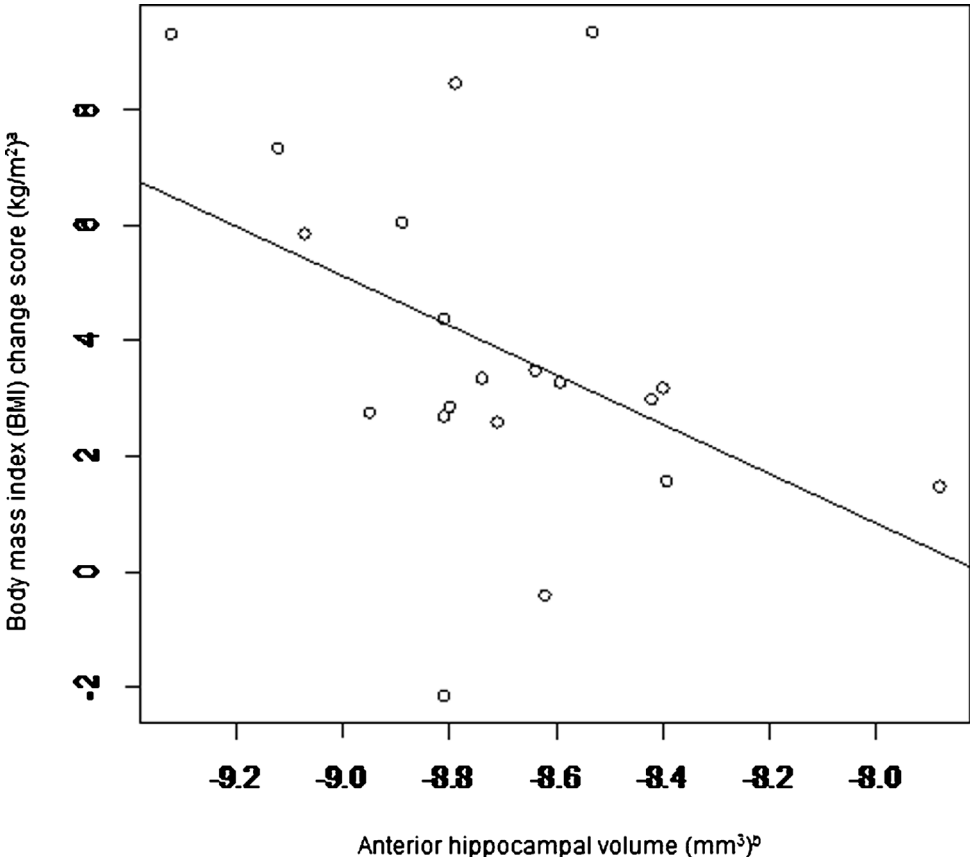

Fig. 2. Scatterplot diagram showing a significant inverse correlation between baseline anterior hippocampal volumes and change in body mass over 12 months of treatment in female firs-episode schizophrenia spectrum disorders (n = 24). BMI change score measured in kilograms (kg) per meter squared (m^2) [kg/m^2] [a]; hippocampal volume (anterior) measured in cubic millimetres (mm^3) [b].

(Davidson et al., 2019). Our findings are therefore in keeping with the known contribution of hippocampal dysfunction to risk for weight gain via abnormal processing and consolidation of food-related memories (Davidson and Jarrard, 1993), ultimately leading to greater responsiveness to food cues, increased appetite, and weight gain (Hargrave et al., 2016; Mestre et al., 2017). In particular our finding of an association between weight gain and the anterior hippocampus is important, since it is more intimately involved in stress sensitivity, mood and emotion via its connectivity with the insula, amygdala and other regions compared to the posterior hippocampus, which is more involved in spatial learning and episodic memory hippocampus (Chase et al., 2015; Zeidman and Maguire, 2016; Dalton et al., 2019).

Higher levels of inflammation in female compared to male patients (Lee et al., 2019) may help explain the sex-specific nature of our findings. In schizophrenia, inflammation has been associated not only with hippocampal dysfunction and memory impairment, but also with risk for treatment-emergent weight gain (Kalmady et al., 2014; Fonseka et al., 2015; Borovcanin et al., 2017). The use of antipsychotics including flupenthixol is associated with down-regulation of inflammation, which could promote weight gain by counteracting anorexigenic signals in the brain. This could then lead to increased appetite and a resultant increase in body weight over the course of treatment. It thus stands to reason that, since baseline inflammation is likely higher in females, greater down-regulation would have a more pronounced effect on appetite and therefore on risk for weight gain.

Importantly, differences in brain-derived neurotrophic factor (BDNF) activity between male and female patients may also be involved. BDNF is known to play an important role not only in hippocampal neurogenesis, but also neurotransmitter metabolism, appetite and energy homeostasis (Rothman et al., 2012). Levels of BDNF are also known to be lower in first-episode psychosis patients compared to controls (Green et al., 2011) a finding which has been associated with poorer cognitive performance as well as lower hippocampus volume (Heitz et al., 2018). Studies have further demonstrated sex influences hippocampal BDNF expression (Yamaura et al., 2013) with lower levels being correlated with weight gain in female, but not male schizophrenia patients (Zhang et al., 2014; Yang et al., 2019). In addition, antipsychotic use in schizophrenia has been found to normalize BDNF levels in men but not in women (Chen and Huang, 2011). Therefore, hippocampal dysfunction at baseline may reflect a decrease in BDNF expression, which then predisposed towards weight gain in female patients in our study. Whatever the mechanisms, our discordant findings between males and females indicate that further research is warranted into the role of sex in the link between hippocampal volume and body mass in schizophrenia.

Strengths of the study include the following: first, we used a first-episode sample, which minimized the effects of illness chronicity and targeted patients most susceptible to antipsychotic associated weight gain (Strassnig et al., 2007). Second, we could exclude the confounding effects of prior treatment exposure, since this was a largely antipsychotic-naive sample. Third, we were able to control for the effects of medication adherence by using a depot formulation antipsychotic. However, we acknowledge several limitations in the current study. Firstly, we only considered baseline hippocampal volumes in patients, since only 38 (42%) patients successfully completed the month 12 imaging assessment. Secondly, our results may not necessarily be generalizable to other study populations with different socioeconomic and nutritional backgrounds. Thirdly, the effect of baseline hippocampal volume as a predictor of weight gain was limited to a relatively small group of female patients ($n = 24$).Lastly, while the use of a single antipsychotic in our study had the advantage of providing standardized treatment, it also means that our results are not necessarily applicable to individuals treated with other antipsychotics.

In conclusion, our study supports the existence of an association between weight gain and baseline anterior hippocampal subfield volumes in first-episode schizophrenia spectrum disorder patients, and that this association is sex-specific. We demonstrated the role of the hippocampus as a predictor of weight gain in female patients, suggesting its involvement in the development of treatment-emergent metabolic syndrome changes. Baseline imaging could hold value in explaining how the connectivity between key brain regions involved in the cognitive, physiological and hedonic control of feeding influences risk for development of antipsychotic-induced weight gain in first-episode schizophrenia. Further studies are needed in order to clarify the sex-specific nature of our findings, as well as to what extent abnormalities of brain structure affect the associations between metabolic syndrome, symptom expression and treatment outcome.

Contributors

All authors contributed equally to the manuscript.

Declaration of Competing Interest

Robin Emsley has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka. Hilmar Luckhoff, Lebogang Phahladira, Freda Scheffler, Stefan du Plessis, Laila Asmal, Riaan Olivier, and Sanja Kilian declare that they have no conflicts of interest.

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CHAPTER SIX

CONCLUSION

6.1. INTRODUCTION

The present chapter provides a narrative synthesis of the main insights gathered as a result of the doctoral research described in this dissertation. Future research avenues are further discussed, and an overall conclusion provided.

6.2. Weight Gain and Clinical Outcome in First-Episode Schizophrenia

In accordance with our primary research objective, we found that the relationship between increased body mass and favourable clinical outcomes described for chronic schizophrenia (Sharma et al., 2014; Raben et al., 2017) also affects first-episode patients (n=106) over the first 12 months of treatment (Chapter II). Importantly, this effect was shown to be independent of the confounding effects of age, sex, substance use, and other metabolic syndrome changes. In addition, we demonstrated an illness-specific association between weight gain and improvement in the disorganized symptom domain of schizophrenia, which was independent not only of the degree of antipsychotic exposure, but also co-treatment with antidepressants and anticholinergic medications (Chapter II).

In most prior outcome studies, chronic patients were with either clozapine or olanzapine, which are known for their propensity to induce weight gain (Sharma et al., 2014; Raben et al., 2017). In contrast, we enrolled first-episode patients treated with flupenthixol decanoate, which is considered relatively more weight-neutral, despite resulting in a significant increase in body mass over 12 months in an overlapping study cohort (Chiliza et al., 2015a). Furthermore, our use of a long-acting injectable antipsychotic allowed us to control for medication adherence (Chapter II) which represented a major strength of our research. Taken together, our findings argue that the association between increased body mass and clinical benefit described for schizophrenia is not just a reflection of higher compliance rates in patients who show a favourable response to treatment in addition to gaining more weight.

Indeed, our use of a depot formulation of treatment provided based on a standardized protocol ensured that we could control for patient adherence. Our research thus supports a fundamental and illness-specific relationship between weight gain and clinical improvement that is not confounded by treatment compliance. In addition to eliminating medication adherence as a potential confound, a similar effect for in-patient hospitalization should be considered. However, we note that the majority of patients (n=85; 67%) in our larger first-episode cohort (n=126) were not hospitalized upon admission. Post-hoc testing did not reveal obvious differences in the socio-demographic or clinical profiles of patients stratified based on the need for in-patient hospitalization. The short duration of in-patient care in those who were hospitalized bears mention, as does the limited extent of treatment exposure prior to admission. This is important, since it can be argued that a longer duration of in-patient care would amount to higher access to psycho-social support as well as increased nutritional support. However, financial support in the form of social grants would be available to all patients following a formal diagnosis of schizophrenia being established. The anticipated effect of in-patient care on access to food and medical care is therefore expected to be limited. That being said, our research emphasizes the specific healthcare needs of vulnerable individuals in our own population. Future studies would do well examine the social determinants of barriers to healthcare access and food security in lower- to middle-income communities.

6.3. Body Mass Index and Clinical Outcome in First-Episode Schizophrenia

In a follow-up study (Chapter III), we showed that the role of weight gain as a favourable prognostic marker is not limited to psychopathology outcomes (Chapter II), but extends to include better overall end-point cognition (MCCB) after 12 months of treatment in first-episode schizophrenia spectrum disorder patients (n=72). This effect remained even when adjusting for relevant clinical (i.e. age, sex, substance use, baseline cognitive scores), metabolic (baseline body mass index) and treatment-related (mean modal antipsychotic dose, duration of exposure) confounders. However, in contrast to global cognitive outcomes

(MCCB), the specific correlation between weight gain and better end-point working memory performance in first-episode patients (n=72) did not remain when adjusting for substance use and baseline body mass index in a linear regression model (Chapter III).

Based on this finding, we performed several post-hoc tests to further explore the associations of body mass index with working memory performance in first-episode patients stratified according to substance use. First, we found that baseline body mass index was significantly lower in substance users compared to non-users (p=0.03). Second, substance use itself was associated with poorer end-point working memory performance (p=0.01), with a significant improvement in this cognitive domain over 12 months of treatment being limited to substance non-users (p=0.02). Third, low baseline body mass index was associated with higher end-point working memory scores in substance non-users, who gained more weight over 12 months of treatment compared to their non-using counterparts. In comparison, low body mass index was associated with poorer end-point working memory performance in substance users, who gained less weight, and showed prevalent weight loss over the course of the study, compared to non-users (Chapter III).

The findings outlined above were deemed in accordance with those reported in an overlapping first-episode patient cohort (n=109), whereby cannabis users gained less weight over 12 months of flupenthixol decanoate treatment compared to non-users (Scheffler et al., 2018). Similar research conducted in first-episode samples also emphasizes the lower propensity for cannabis-using patients to either gain weight or develop the metabolic syndrome as composite entity (Stiles et al., 2020). Failure to gain weight in some first-episode patients who use cannabis could be related in part to differences in clinical outcome evident when compared to non-users, including a higher risk of relapse, despite similar overall trajectories for psychopathology and depressive symptom outcomes overall between the two groups (Scheffler et al., 2020). The notion that low body mass index as an intrinsic metabolic feature of schizophrenia (Shah et al., 2019) constitutes an unfavourable clinical marker is further evidenced by its associations with a shorter time to relapse (Stauffer et al.,

2011), longer time to respond to treatment (Schwarz et al., 2012), and treatment failure (Chiliza et al., 2015b) in schizophrenia patients.

It is further noted we found a higher prevalence of cannabis use among male compared to female first-episode patients across different sub-studies (Chapter II, IV). This should be highlighted, since male sex is a known risk factor for low body mass in schizophrenia (Wang et al., 2020) as well as healthy controls (Chapter IV). In addition, male patients often experience more pronounced negative symptoms, lower psycho-social functioning, and a poorer response to treatment overall compared to female patients (Ochoa et al., 2012; Li et al., 2016). In addition, some research (Miettunen et al., 2018; Riecher-Rossler et al., 2018) suggests that the age of onset is earlier in male compared to female patients, although this finding has not been replicated in all studies to date (Venkatesh et al., 2008; Naqvi et al., 2010). Nevertheless, and earlier age of onset is still thought to shape the clinical expression and temporal course of illness in schizophrenia spectrum disorders (Kao and Liu, 2010; Immonen et al., 2017).

It is thus at times difficult to disentangle the associations between cannabis use, low pre-treatment body mass and failure to gain weight to the same degree as non-using patients from the potential confounding effects of biological sex and age of onset. This complexity was identified as an important factor to be considered in future studies exploring the effects of ongoing cannabis use on the temporal course of illness and clinical outcomes in first-episode patients in relation to important socio-demographic (e.g. biological sex) and treatment-related (e.g. changes in body mass index) confounders.

In particular, there is a need to examine the inverse correlation between body mass index and negative psychopathology evident in our patient sample (Chapter IV). This is important, since sex-based differences in both negative symptoms and rates of comorbid substance abuse have been described for schizophrenia (Abel et al., 2010; Li et al., 2016). In this context, our understanding of this clinical domain, its assessment, and effects on outcome

have evolved over time (Correll and Schooler, 2020). For example, the distinction between its expressive and experiential aspects is now recognized. In addition, several novel instruments have been developed to support to examination of negative symptoms in both a clinical and research setting (Kirkpatrick et al., 2011; Kring et al., 2013). Future studies would do well to examine different aspects of clinical outcome (e.g. degree of reduction, time to improvement, and negative symptom persistence) in relation to its predictors and clinico-biological correlates in first-episode schizophrenia.

In addition, it will be important to extend our focus on the characterization of cannabis use in relation to metabolic status and clinical outcomes in schizophrenia. In particular, we aim to calculate a continuous measure of ongoing use based on the number of positive urine screening results over a specific time period. In addition, more examination of both cessation and relapse of use are envisioned. In the near future, it will also be possible to perform cannabinoid profiling (drug) and pharmacogenomics testing (host) in order to facilitate risk-benefit stratification in both health and disease. This could represent an important step towards ethical interventional research including the use of certain cannabinoids to improve treatment outcomes in first-episode schizophrenia.

6.4. Brain Structural and White Matter Connectivity Correlates of Body Mass Index in First-Episode Schizophrenia

In order to better understand the role of body mass index as a predictor of illness severity and clinical outcome, we decided to incorporate a structural neuroimaging component as part of the multi-modal assessment of metabolic syndrome risk factors in our first-episode patient cohort. In lieu of selecting global brain structural measures (e.g. total cortical gray or white matter volume, subcortical gray matter), we decided to first focus our attention on diffusion tensor imaging (DTI) as a valuable approach used for the in vivo assessment of white matter connectivity(Chapter IV).

In particular, we selected fronto-limbic white matter tracts based on a priori knowledge of their roles in connecting diverse brain regions involved in the physiological (e.g. hypothalamus, brainstem), hedonic (ventral striatum, nucleus accumbens, ventral tegmental area) and cognitive-emotional (amygdala, hippocampus) control of feeding in humans as part of a "core eating network" (Chen et al., 2016). We elected to focus on fractional anisotropy (FA) as our main measure of interest for the following tracts: the genu, body and splenium of the corpus callosum, fornix, left and right tapetum, left and right superior fronto-occipital fasciculus, left and right fornix crus/stria terminalis, left and right cingulum bundle, left and right cingulum of the hippocampus, as well as the left and right uncinate fasciculus (Chapter IV).

In a multivariate model, we demonstrated a significant effect for body mass index across all fronto-limbic white matter tracts of interest in patients (low body mass index, low FA) versus controls (high body mass index, low FA), adjusting for age, sex, and cannabis use. In particular, we found that lower body mass index in first-episode schizophrenia spectrum disorder patients correlated with decreased FA for the genu of the corpus callosum and left tapetum in particular (Chapter IV). Our inclusion of a structural neuroimaging component alongside existing socio-demographic, clinical and metabolic data thus provided important evidence to suggest that the role of low baseline body mass index as a putative adverse prognostic marker has a neurobiological underpinning.

Based on this foundational research, we thus extended our neuroimaging assessment to include structural magnetic resonance imaging (MRI) of subcortical brain regions involved in the regulation of appetite, satiety and reward, subsumed as part of the "core eating network" in humans (Chen et al., 2016). Most of these subcortical structures are known to be connected via the same fronto-limbic white matter tracts we explored using DTI (Chapter IV), and included the amygdala, brainstem, ventral tegmental area, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, ventral diencephalon and ventral striatum as regions of interest. In particular, we focused our attention on the hippocampus,

an area known to be active at the crucial interface between the physiological, hedonic, and cognitive control of appetite, satiety and reward (Chapter V).

The decision to include the hippocampus as our main region of interest was further motivated by the development of novel software techniques which allow an unprecedented view of the individual subfields which comprise the hippocampus. We were thus interested in the associations of the hippocampus and its subfields with baseline body mass index and its temporal evolution over 12 months of treatment in our first-episode patient cohort (n=90) compared to healthy controls (n=92). The anterior hippocampus in particular emerged as a sex-specific predictor of weight gain in first-episode schizophrenia spectrum disorder patients, independent of age, substance use, or treatment duration. In particular, lower volumes for the subiculum, cornus ammonis (CA) 1 and 3 subfields were associated with a greater increase in body mass index over 12 months of treatment in female patients (Chapter V).

In summary, the inclusion of a neuroimaging component to our research helped to reveal the brain structural underpinnings of body mass index and its temporal evolution over 12 months of treatment in first-episode schizophrenia spectrum disorders. Insight gathered as a result of this process prompted an initial characterization of important brain structural correlates which could help explain the unfavourable prognostic role of low body mass index and/or failure to gain weight in first-episode schizophrenia spectrum disorder patients (Chapters III, IV). In addition, structural neuroimaging assisted us in the identification of brain regions including the hippocampus which could play a role in the known differences in weight gain trajectories evident between male and female schizophrenia patients (Chapter V).

6.5. Future Research Directions

Our research uncovered important relationships between weight gain and clinical improvement over the first 12 months of treatment in first-episode schizophrenia spectrum disorder patients treated with flupenthixol decanoate. Nevertheless, it also emphasized our research shortcomings, including the limited sample sizes noted for each of our individual studies included in this dissertation. General considerations including the need to extend our research scope and focus on similar patients enrolled as part of overlapping project cohorts should thus be considered across all specific future directions discussed below. That being said, we also note the sample size in terms of absolute number should be weighed against this being a single-site cohort study including well-characterized patients subjected to careful follow-up over time. In addition, our findings indeed provide the scientific rationale and motivation for further research into the long-term evolution of metabolic syndrome risk factors and their associations with treatment outcome in our first-episode patient sample.

6.5.1. Intrinsic Weight Gain Trajectories and Long-Term Outcome in First-Episode Schizophrenia

In the context of cardiovascular research, an emerging body of evidence suggests that obesity is associated with a favourable prognosis and decreased mortality risk in patients with established ischemic heart disease (Gruberg et al., 2002). In recognition of this apparent “obesity paradox”, researchers started to draw a theoretical distinction between 1) metabolically healthy obesity, characterized by its association with other metabolic syndrome changes, ectopic fat deposition, immune dysregulation, altered adipocytokine expression, low-grade inflammation and oxidative stress, and 2) metabolically unhealthy obesity, characterized by a dissociation from other metabolic syndrome changes, preservation of normal immune functioning, an intact response to insulin, as well as a favourable metabolic profile (Roth et al., 2016).

Little is however known about the long-term evolution of treatment-emergent metabolic syndrome risk factors in schizophrenia (Strassnig et al., 2017). It is plausible that a similar approach to that used in cardiovascular research (Vecchie et al., 2018) could provide novel insights into how different weight gain trajectories affect long-term clinical outcomes in first-episode schizophrenia spectrum disorders. To date, we have collected comprehensive clinical and metabolic data on our first-episode patient cohort over the first 24 months of treatment. In an important first step, we aim to determine whether weight gain beyond the first year of treatment continues unabated, or rather tends to level off over time (Mustafa et al., 2019). Since serum glucose levels remained relatively stable over the first 12 months of treatment in our first-episode patient cohort (Chiliza et al., 2015a), an important second step would be to determine whether risk for Insulin Resistance (IR) and type II Diabetes Mellitus (DM II) increases over a more chronic period of treatment exposure (Pillinger et al., 2017; Jeong et al., 2018).

Here, we anticipate that a pronounced increase in body mass index, that reaches an initial plateau, in addition to being dissociated from other metabolic syndrome changes, would represent a favourable weight gain profile associated with a good overall prognosis (Bhansali et al., 2017; Raben et al., 2017). In contrast, a more insidious, chronic and persistent elevation in body mass index beyond the first 12 months of treatment, that clusters with other metabolic syndrome features, could rather represent an opposing weight gain profile associated with an unfavourable prognosis and poorer treatment outcomes (Roth et al., 2016).

In such patients, poor diet and lifestyle habits are believed to compound risk for ectopic fat deposition associated with altered adipocytokine expression, aberrant immune regulation, chronic low-grade inflammation, and oxidative stress (Roth et al., 2016). These changes can ultimately lead to failure of compensatory mechanisms which in turn causes acute metabolic changes that were once favourable to become deleterious (Vecchie et al., 2018). If such protective mechanisms are no longer intact, and these changes occur over a sufficient

timeframe, increased visceral adiposity may drive metabolic abnormalities linked to an unfavourable clinical prognosis, poor mental health, decreased levels of functioning, and poor quality of life in the long-term (Agid et al., 2013; Kritharides et al., 2017).

However, we also emphasize that a broad distinction between two weight gain trajectories and their association metabolic changes being consistently “favourable” versus “unfavourable” could belie a more complex relationship between body mass index, clinical improvement and treatment effects in first-episode schizophrenia spectrum disorders (Wang et al., 2020).

6.5.2. Evolution of Lipid Abnormalities and Clinical Outcome in First-Episode Schizophrenia

In our first-episode patient cohort (n=107), treatment with flupenthixol depot over 12 months resulted in a significant increase in serum triglycerides, as well as a significant decrease in high-density lipoprotein (HDL) cholesterol levels (Chiliza et al., 2015a). Following the identification of different weight gain trajectories in relation to longer-term clinical outcomes, an important next step would be to extend our focus to also examine the evolution of sub-clinical lipid abnormalities using our 24-month dataset. First, we are interested in the proposed co-occurrence of elevated triglycerides with decreased total and low-density lipoprotein (LDL) cholesterol levels described for treatment-naive first-episode schizophrenia patients (Misiak et al., 2017; Pillinger et al., 2017) and its effects on clinical outcome over the first 24 months of treatment in our patient sample.

The directional and specific natures of such lipid profile alterations are not clear-cut, and could be considered as being dependent on disease stage and illness chronicity, among other factors. For example, in a meta-analysis of 14 studies conducted by Kim and colleagues (2019), the authors presented the argument that an elevation in triglyceride levels is associated with a favourable response to treatment in schizophrenia patients, independent of the specific antipsychotic prescribed, as well as co-treatment with lipid-lowering statins. In

contrast, a more recent prospective evaluation of outcome data obtained from a first-episode psychosis patient sample (n=749) provided evidence that rather substantiates the role of increased triglycerides at baseline as being consistent with an unfavourable long-term prognosis, independent of body mass index (Osimo et al., 2020).

In a similar fashion, several studies have also found that low cholesterol levels are associated with increased risk for suicide, higher levels of aggression, and impulsivity in first-episode schizophrenia (Atmaca et al., 2003, 2007; Kavoor et al., 2017). In comparison, opposing studies rather suggest that high cholesterol levels are associated with more severe psychopathology (Devanarayanan et al., 2016), non-remission (Stratta and Rossi 2013), and higher depressive symptom severity (Fang et al., 2019; Gohar et al., 2019) in chronic as opposed to first-episode schizophrenia patients. Future research would therefore do well to determine whether possible increases in certain lipids including cholesterol levels following initial treatment exposure in first-episode patients represent a “return to baseline”, or aggravation of future cardio-metabolic risk, as well as how this relates to the stage of the disease, as well as the duration of treatment. In brief, the beneficial versus detrimental relationships of high versus low lipid levels is not clear-cut, and likely dependant on pre-treatment levels, illness stage, the specific lipid fraction, and other metabolic syndrome features (IR, DM II) present, among other factors.

In this context, it will soon be possible to perform more extensive lipid profiling using existing stored biological samples collected from our first-episode patient cohort described in this dissertation at an affordable price point, and use this data to predict treatment outcomes and tailor patient management based on individualized needs of care. For example, Tessier et al., (2016) used red blood cell membrane lipidomics to characterize specific phospholipid and fatty acid profiles in schizophrenia patients compared to healthy controls. These different lipid clusters showed distinct relationships with psychopathology severity and cognitive symptoms in the patient group. In a subsequent study, Aquino and colleagues (2018) performed lipidomics profiling using plasma samples collected from schizophrenia

patients (n=54) treated over six weeks with a second-generation antipsychotic. This approach allowed the researchers to differentiate responders from non-responders for olanzapine, risperidone and quetiapine based on plasma lipid compound levels collected at baseline. Lastly, it has most recently been proposed that researchers can combine psychopathology scores and metabolic profiling in order to categorize patients with dissimilar clinical diagnoses (first-episode psychosis, schizophrenia, bipolar disorder) into prognostic subgroups based on their expected temporal course of illness following remission (Joaquim et al., 2020).

6.5.3. Identification of Biological Mechanisms Underscoring the Relationships between Body Mass and Treatment Outcome in First-Episode Schizophrenia

Following the characterization of different proposed weight gain trajectories in relation to other metabolic syndrome changes and their effects on clinical outcome, we aim to put emphasis on the identification of plausible biological mechanisms underscoring these associations. In particular, a major focus will be on blood-based biomarkers including hormones and signalling proteins involved in appetite regulation and their associations with body mass, weight gain and treatment outcome in our first-episode patient sample (Chapters II, III).

Initial exposure to antipsychotics, as well as the associated development of weight gain in treatment-naive schizophrenia patients, exerts individual and additive effects on the expression of both pro- and anti-inflammatory cytokines (Haring et al., 2015; Petrikis et al., 2015; Juncal-Ruiz et al., 2018). These changes in cytokine profiles could be related to improvement in psychopathology severity associated with weight gain in treatment-naive first-episode schizophrenia patients (Haring et al., 2015; Dahan et al., 2018). In a similar fashion, an elevation in leptin and decrease in adiponectin as well as ghrelin levels over the initial course of treatment in first-episode schizophrenia patients could in part mediate a proposed favourable association between weight gain and psychopathology improvement

(Atmaca et al., 2003, 2007; Perez-Iglesias et al., 2008; Basoglu et al., 2010; Nurjono et al., 2014; Balotsev et al., 2019).

However, the complex inter-active effects of both antipsychotic exposure and weight gain on the trajectories of these diverse cellular mediators remain poorly understood and subject to further inquiry. Importantly, acute alterations in certain hormones and cytokines (e.g. IL-2, IL-6) over the course of treatment in first-episode schizophrenia could represent a state-related phenomenon, while persistent elevation in other inflammatory markers such as tumour necrosis factor alpha (TNF-a) and C-reactive protein (CRP), compounded by weight gain may be largely "trait-related" (Miller et al., 2011; Fernandes et al., 2016; Capuzzi et al., 2017). In addition, elevated CRP levels have been correlated with more severe negative symptoms, catatonic features and higher levels of aggression (Barzilay et al., 2016; Orsolini et al., 2018). This hints at more complex, inter-related metabolic pathways linking lipid abnormalities, inflammation and aberrant immune activation with increased illness severity in schizophrenia.

6.5.4. Characterization of Brain Structural Changes in Relation to Metabolic Risk and Clinical Outcome in First-Episode Schizophrenia

Our research to date has identified promising subcortical brain regions and white matter tracts known to form part of a "core eating network" in humans (Chen et al., 2016) as illustrated in Figure 1. The doctoral research presented in this dissertation provides the scientific rationale for extending our focus on structural neuroimaging to include connectomics approaches used to evaluate brain-based biomarkers in relation to metabolic risk and treatment outcome in first-episode schizophrenia spectrum disorders (Clementz et al., 2016). The need to define these neurobiological profiles based in part on brain structural assessment is based in part on their limited overlap with exiting clinical models for schizophrenia, which often do not adhere to existing diagnostic structures for the disorder (Clementz et al., 2016).

In a recent study, Chand and colleagues (2020) used machine learning to describe two distinct brain structural signatures using structural MRI data obtained from schizophrenia patients (n=307) and healthy controls (n=364). In brief, the first brain structural signature was characterized by widespread grey matter volume reductions (including the medial frontal, temporal and insular cortices) which correlated with a longer duration of illness, poorer educational attainment, and poorer premorbid adjustment. In comparison, the second brain structural signature was characterized by relatively normal and stable neuroanatomy, despite increased basal ganglia and internal capsule volumes, which could not be ascribed to treatment exposure (Chand et al., 2020). In this setting, we aim to use a similar approach to explore the effects of treatment exposure on brain structure in our first-episode patient cohort. In particular, we aim to focus on three major structural neuroimaging outcomes, i.e. global cortical thickness, total white matter, and basal ganglia volumes. In addition, we aim to explore how these associations are related to clinical outcomes and side-effect profiles over 24 months of treatment.

In a follow-up step, we aim to use connectomics data to understand these proposed biotypes in terms of real-world interconnected brain network (Crossley et al., 2017). In an earlier study by Zalesky and colleagues (2012), the authors used network-based statistics to characterize impaired connectivity in schizophrenia patients as an expansively disrupted brain sub-network which mostly consisted of fronto-temporal and occipito-temporal disconnections. Using our available neuroimaging data obtained across two first-episode patient cohorts, we aim to assess path lengths (i.e. distances between each node pair) and then calculate both global and local efficiency as common measures used in prior studies of schizophrenia patients (Zalesky et al., 2012; Zhang et al., 2015; Crossley et al., 2017) with mixed results. Importantly, the connections between brain regions expressed as different connectivity profiles may assist clinicians one day in disease staging, clinical prognostication and monitoring of treatment course (Griffa et al., 2019).

That being said, we do acknowledge that the postulated “core eating network” (Chen et al., 2016) remains to be extensively validated in a formal manner. Nevertheless, the present neuroimaging research provides important evidence to support the involvement not only of specific sub-cortical brain regions in the regulation of appetite, satiety and reward (Chapter V) but also the white matter tracts that connect them (Chapter IV). It is envisioned that extension of our brain structural imaging research over time will reveal novel insights into the regulation of these inter-related networks towards the standardization of specific brain architectures of relevance to our own setting and population samples.

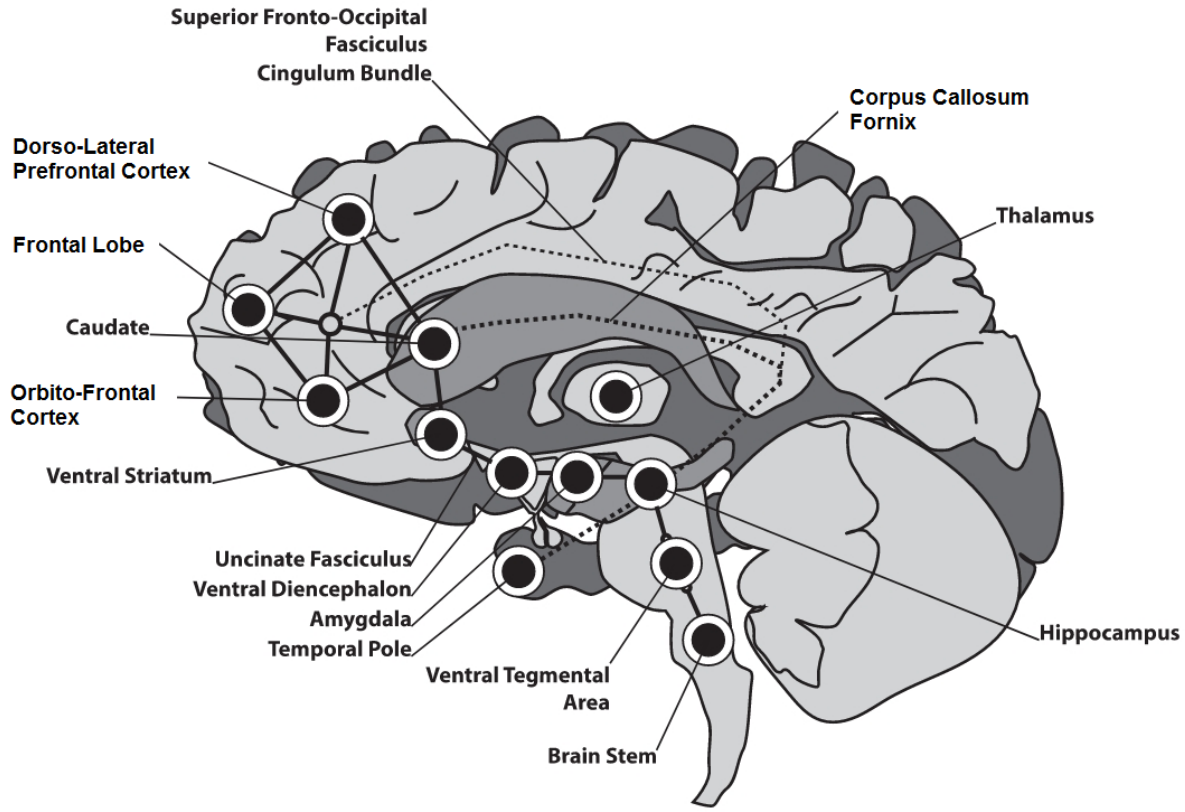

Figure 1. Diagrammatical representation of cortical and sub-cortical neurobiological regions implicated as part of an extended "core eating network" (CEN) in humans, including the white matter tracts which connect these diverse brain areas involved in the regulation of appetite, satiety, emotion, and reward. The white matter tracts overlap with those identified and described in our DTI study (Chapter V). The cortical and sub-cortical areas were mostly selected from available regions of interest (ROI) we considered in sub-study IV (Chapter V) where we elected to focus on the hippocampus. The white matter tracts visible in this diagram include the superior fronto-occipital fasciculus, corpus callosum (which includes the genu, body and splenium), fornix (including fornix crus/stria terminalis), cingulum bundle, and uncinate fasciculus. The cortical areas include the prefrontal lobe, orbito-frontal cortex, dorso-lateral prefrontal cortex, and temporal pole. The sub-cortical areas included the caudate, ventral striatum, amygdala, brain stem, ventral tegmental area, ventral diencephalon, and thalamus (source: original diagram created by author).

6.6. GENERAL CONCLUSIONS

In conclusion, our findings suggest that weight gain over the first 12 months of assured treatment is a predictor of favourable clinical outcomes in first-episode schizophrenia spectrum disorders. This effect extends across multiple domains and is not a reflection of treatment compliance, but rather hints at complex inter-relationship between metabolic syndrome risk factors, clinical presentation and outcome in first-episode schizophrenia. In particular, involvement of brain structure and the connection between different regions of a "core eating network" in our patient sample constitutes an important research development. In addition, we provide novel evidence in support of low body mass index, and by extension, failure to gain weight as unfavourable prognostic markers in first-episode patients, particularly those who use substances. Our research thus provides the scientific basis for an extended application of metabolic assessment beyond cardiovascular risk stratification to include clinical prognostication and prediction of treatment outcome. The concurrent assessment of clinical and metabolic features in relation to brain structure and function could hold promise in optimizing treatment based on individual patient needs in those with first-episode schizophrenia spectrum disorders.

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APPENDIX A

ETHICS APPROVAL LETTER

UNIVERSITEIT
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Health Research Ethics Committee (HREC)

Approval Notice

New Application

17/09/2018

Project ID :6144

HREC Reference #: S18/02/040 (PhD)

Title: Metabolic syndrome risk factor associations with clinical, functional and cognitive outcomes during the first year of treatment in schizophrenia spectrum disorders

Dear Dr. Hilmar Luckhoff,

The **Response to Modifications** received on 13/09/2018 16:08 was reviewed by members of **Health Research Ethics Committee 2 (HREC2)** via **expedited** review procedures on 17/09/2018 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **This project has approval for 12 months from the date of this letter.**

Please remember to use your Project ID [6144] on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/6144

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mr. Francis Masiye ,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number: IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

APPENDIX B

TURNITIN REPORTS

PLAGIARISM REPORT

The final plagiarism report outlined and summarized for the doctoral studies described in this dissertation was created based on its full contents excluding the individual sub-studies in their official published format. This executive decision was motivated by the observation that inclusion of said publications resulted in a disproportionately high similarity index due to their contents being picked up as falling outside the contents of the dissertation. It was therefore elected to exclude the formal publications from the final dissertation submitted via the Turnitin portal. The final index score is therefore presented as a more appropriate reflection of the similarity of the research to existing publications and online sources. This report also represents the final scores obtained following resubmission of the revised dissertation submitted to the doctoral office following independent examiner review.

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